ctos®

Virtual Annual Meeting

November 18–21, 2020

2020 CTOS President

Kirsten Sundby Hall, MD, PhD

2020 CTOS Program Chairs

Margaret von Mehren, MD

Inga-Marie Schaefer, MD

Silvia Stacchiotti, MD

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The Connective Tissue Oncology Society
greatly appreciates your support of the 2020 Annual Meeting. Your funding is vital and will advance the medical science and care of patients with bone and soft tissue tumors.

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Dear Colleagues,

We are very excited and proud to welcome you to the 2020 CTOS Virtual Meeting from November 18th-21st, marking the 25th anniversary of the society!

The pandemic forced us to convert the initially planned in-person meeting to a web conference. We are grateful that our community is supporting this virtual meeting with a continued sense of collegiality and friendship that is key to the success of CTOS. We look forward to connecting with all of you and the sarcoma groups around the world.

We will celebrate the growth of CTOS over the past decades. Founded by a small group of visionaries, CTOS has evolved into the global sarcoma society with yearly annual meetings involving multiple disciplines. These meetings have always been a wonderful opportunity for networking and have fostered the exchange of ideas and vivid discussions to advance the field of sarcoma diagnosis and clinical management.

The program was developed to feature proffered abstract presentations and lectures, providing a mixture of "science" and "education". Sessions will focus on a disease entity or family of entities, rather than on disciplines, and will include abstracts on both preclinical, translational and clinical aspects.

To make the best use of our time together, all posters and abstract presentations will be available for registrants prior to the meeting. You are encouraged to view and download the recorded presentations starting on November 11th, one week in advance of the conference.

During the meeting, oral abstract sessions will start with a 20-minute presentation by an expert sarcoma discussant putting the selected abstracts into context. This will be followed by a 40-minute live discussion led by the session chair and including the abstract presenters and a panel of sarcoma experts. Questions will be raised by the members of the roundtable and from you the audience: please submit your questions through the chat function!

We especially invite junior sarcoma clinicians, diagnosticians, and researchers to attend and contribute to this meeting! CTOS is committed to the education of the next generation of sarcoma experts, who will be crucial in further advancing this field. We will have a "Meet-the-Experts" session at the end of the first day with interactive case discussions between panel experts, patient representatives and the audience. Please register in advance for these session as spots are limited.

We are confident that this meeting will stimulate interdisciplinary discussions on timely scientific and educational topics, harmonize our views and practices throughout the world, raise open questions to be addressed in future years, and enable us to continue our collaborative efforts across borders and oceans. The success of this meeting - as of our global sarcoma community - will depend on the contributions of each one of you.

We thank all of you who have made this meeting possible and look forward to seeing and hearing from you during the meeting!

Sincerely,

Margaret von Mehren
Inga-Marie Schaefer
Silvia Stacchiotti

CTOS 2020 Board of Directors

2020 Virtual Annual Meeting

Schedule at a Glance

ALL TIMES ARE EASTERN STANDARD TIME (EST)

Wednesday, 18 November, 2020

8:00 am - 11:00 am	**TARPSWG Meeting** (email: tarpswg@gmail.com) – Chair: Alessandro Gronchi
11:00 am - 1:00 pm	**Ultra Rare Sarcoma Meeting –** Chair: Silvia Stacchiotti
1:00 pm - 3:00 pm	**SARC Meeting** *(see page vi)*
3:00 pm - 5:00 pm	**SELNET Meeting: State of the Art of Management for Localized STS in Limbs and Retroperitoneum –** Chair: Javier Martin-Broto
4:00 pm - 4:30 pm	– Symposium – VITRAKVI® (LAROTRECTINIB) OVERVIEW AND CASE PRESENTATION

Thursday, 19 November, 2020

8:00 am - 9:00 am	– Session 1 – OPENING CEREMONY INTRODUCTION TO CTOS 2020 President: **Kirsten Sundby Hall** Program Chairs: **Silvia Stacchiotti**, **Margaret von Mehren**, **Inga-Marie Schaefer** 25 YEAR RETROSPECTIVE Presenter: **Shreyas Patel**
9:00 am - 10:00 am	– Session 2 – IMMUNOTHERAPY IN SARCOMA: ALVEOLAR SOFT PART SARCOMA, CLEAR CELL SARCOMA, SYNOVIAL SARCOMA
10:00 am - 10:30 am	Morning Break
10:30 am - 11:30 am	– Special Awards Session – YOUNG INVESTIGATOR AWARD WINNERS LIDDY SHRIVER EARLY RESEARCH AWARD WINNER BASIC SCIENCE SARCOMA RESEARCH AWARD WINNERS
11:30 am - 12:30 pm	– Session 3 – NATIONAL LEIOMYOSARCOMA FOUNDATION RESEARCH GRANT LEIOMYOSARCOMA AND UNDIFFERENTIATED PLEOMORPHIC SARCOMA

Thursday, 19 November, 2020

12:30 pm - 1:30 pm — – Session 4 –
OSTEOSARCOMA AND PEDIATRIC BONE SARCOMAS

1:30 pm - 2:30 pm — MEET THE EXPERTS
Multidisciplinary Discussion of Clinical Cases

Room 1:	Room 2:	Room 3:
GIST	Bone Sarcomas	Soft Tissue Sarcomas

2:30 pm - 3:30 pm — CTOS Executive Committee Meeting

3:00 pm - 4:30 pm — – Symposium –
THE CASE FOR CHALLENGING CONVENTIONAL CARE IN TENOSYNOVIAL GIANT CELL TUMOR: INSIGHTS ON INTEGRATING TARGETED THERAPY INTO MULTIMODAL MANAGEMENT

Friday, 20 November, 2020

8:00 am - 9:00 am — – Session 5 –
"WHAT IS NEW IN SARCOMA PATHOLOGY AND MOLECULAR DIAGNOSTICS"

9:00 am - 10:00 am — – Session 6 –
CHONDROSARCOMA, CHORDOMA, AND OTHER BONE TUMORS

10:00 am - 10:30 am — Morning Break

10:30 am - 11:30 am — – Session 7 –
LIPOSARCOMA

11:30 am - 12:30 pm — – Session 8 –
GIST

12:30 pm - 1:30 pm — HERMAN SUIT LECTURE – GENETICS, GENOMICS AND SARCOMAS
David Thomas

1:30 pm - 2:30 pm — VIRTUAL GET-TOGETHER

2:30 pm - 3:30 pm — CTOS Board of Directors Meeting

3:00 pm - 4:00 pm — – Symposium –
PERSONALIZING AND PROLONGING CARE IN GIST:
EXPERT GUIDANCE ON INTEGRATING NEW TKI STRATEGIES

Saturday, 21 November, 2020

8:00 am - 9:00 am — – Session 9 –
EPIGENETICALLY DRIVEN SARCOMAS

9:00 am - 10:00 am — – Session 10 –
ADVANCES IN ANGIOSARCOMA, PECOMA, AND CLEAR CELL SARCOMA

10:00 am - 10:30 am — Morning Break

10:30 am - 11:30 am — NINA AXELRAD LECTURE – EVOLUTION OF DOGMAS IN SARCOMA SURGERY
Sylvie Bonvalot

Saturday, 21 November, 2020

11:30 am - 12:30 pm	– Session 11 – RHABDOMYOSARCOMA AND EWING SARCOMA
12:30 pm - 1:30 pm	– Session 12 – LOCALLY AGGRESSIVE MESENCHYMAL TUMORS: DESMOID TUMOR, DIFFUSE-TYPE GIANT CELL TUMOR Lecture: RECENT UPDATES IN LOCALLY AGGRESSIVE MESENCHYMAL TUMORS: DESMOID TUMOR, DIFFUSE-TYPE GIANT CELL TUMOR **Mrinal Gounder**
1:30 pm - 2:00 pm	CLOSING REMARKS President: **Kirsten Sundby Hall** Program Chairs: **Silvia Stacchiotti**, **Margaret von Mehren**, **Inga-Marie Schaefer**
2:00 pm - 3:00 pm	CTOS Members' Business Meeting

SARC Semiannual Meeting

Wednesday, November 18 **1:00 to 3:00 pm (EST)**

Agenda

Chawla-Rosenfeld Developmental Therapeutics Symposium

Tumor Microenvironment: Potential Impact on Immunotherapy in Sarcomas

1:00 pm - 1:10 pm (EST) *(Live)*	Introduction	Moderators: **Robert Maki, MD, PhD** University of Pennsylvania Robert.Maki@Pennmedicine.upenn.edu **Missy Burgess, MD** University of Pittsburgh burgessma@upmc.edu
1:10 pm - 1:30 pm *(Recorded)*	Heterogeneity of Cancer Associated Fibroblasts in Pancreatic Ductal Adenocarcinoma	**Sandeep Nadella, MD** Cold Spring Harbor Laboratory nadella@cshl.edu
1:30 pm - 1:50 pm *(Recorded)*	Myeloid-derived Suppressor Cells in Regulation of Immune Responses in Cancer	**Dmitry Gabrilovich, MD, PhD** AstraZeneca dmitry.gabrilovich@astrazeneca.com
1:50 pm - 2:10 pm *(Recorded)*	Immune Classes of Soft-Tissue Sarcoma: B Cells and Tertiary Lymphoid Structures Associate with Survival and Response to Immunotherapy	**Florent Petitprez, PhD** University of Edinburgh Florent.Petitprez@ligue-cancer.net
2:10 pm - 2:30 pm *(Recorded)*	The Sarcoma Immune Microenvironment	**Seth Pollack, MD** Fred Hutchison Cancer Research Center spollack@fredhutch.org
2:30 pm - 3:00 pm *(Live)*	Discussion: Q & A	**Panel**
3:00 pm	Adjourn	

DECIPHERA IS ADVANCING

THE TREATMENT OF TENOSYNOVIAL GIANT CELL TUMORS (TGCT)

Deciphera Pharmaceuticals is currently developing DCC-3014 as a potential treatment for TGCT

TGCT is a rare disease caused by translocation in colony-stimulating factor 1 (CSF1) gene resulting in overexpression of CSF1 and recruitment of colony-stimulating factor 1 receptor (CSF1R)-positive inflammatory cells into the lesion. TGCT is also known as giant cell tumor of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS).[1]

DCC-3014 is an investigational, orally-administered switch-control tyrosine kinase inhibitor specifically designed to selectively and potently inhibit CSF1R. Deciphera is currently studying DCC-3014 in an international, multicenter, open-label Phase 1/2 study, and is currently enrolling patients with TGCT.[1,2]

The therapeutic potential of DCC-3014 is the focus of a multicenter, Phase 1/2 open-label study[1,2]

- This is an international, multicenter, open-label Phase 1/2 study of DCC-3014 to assess its safety, efficacy, pharmacokinetics, and pharmacodynamics in patients with advanced tumors and TGCT. At this time, the study is only enrolling TGCT patients
- **Phase 1 dose escalation** includes both malignant solid tumor and TGCT patients to determine the recommended Phase 2 dose (RP2D) and maximum tolerated dose (MTD)
- **Phase 2 dose expansion** focuses on patients with confirmed histological diagnosis of TGCT not amenable for surgery, and consists of two cohorts:
  - Cohort A: TGCT patients who have not received prior systemic treatment with anti-CSF1 or anti-CSF1R therapy; previous therapy with imatinib and nilotinib is allowed
  - Cohort B: TGCT patients with prior systemic treatment with anti-CSF1 or anti-CSF1R therapy, with the exception of imatinib or nilotinib

For more information about the clinical trial design, please visit **www.clinicaltrials.gov** (NCT03069469).
For specific questions related to the DCC-3014 study, please contact **clinicaltrials@deciphera.com**.

References: 1. Wilky B, Taylor M, Bauer T, et al. Phase 1 study of DCC-3014 to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with malignant solid tumors and diffuse-type tenosynovial giant cell tumor. Poster presented at: Connective Tissue Oncology Society Annual Meeting; November 2019; Tokyo, Japan. **2.** Study of DCC-3014 in Patients With Advanced Tumors and Tenosynovial Giant Cell Tumor. ClinicalTrials.gov identifier:NCT03069469. Accessed October 12, 2020. https://www.clinicaltrials.gov/ct2/show/NCT03069469.

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3:00 pm - 5:00 pm	**SELNET Meeting: State of the Art of Management for Localized STS in Limbs and Retroperitoneum –** Chair: Javier Martin-Broto

4:00 pm - 4:30 pm

– Symposium –

VITRAKVI® (LAROTRECTINIB) OVERVIEW AND CASE PRESENTATION

Presenter: **Noah Federman, MD,** Director of Pediatric Bone and Soft Tissue, Sarcoma Program at UCLA Medical Center

Sponsored By: BAYER

Thursday, 19 November, 2020

8:00 am - 9:00 am

– Session 1 –

OPENING CEREMONY INTRODUCTION TO CTOS 2020

President: **Kirsten Sundby Hall**
Program Chairs: **Silvia Stacchiotti**, **Margaret von Mehren**, **Inga-Marie Schaefer**

25 YEAR RETROSPECTIVE

Presenter: **Shreyas Patel**

9:00 am - 10:00 am — – Session 2 –

IMMUNOTHERAPY IN SARCOMA: ALVEOLAR SOFT PART SARCOMA, CLEAR CELL SARCOMA, SYNOVIAL SARCOMA

Chair: **Seth Pollack**
Discussant: **Breelyn Wilky**
Panelists: **Armelle Dufresne**, **Bob Maki**, **Enrico Grignani**
Presenters: **Akira Kawai**, **Nadia Hindi**, **Sandra d'Angelo**, **Brian van Tine**

Paper #01 3421748

EFFICACY AND SAFETY OF NIVOLUMAB MONOTHERAPY IN PATIENTS WITH UNRESECTABLE CLEAR CELL SARCOMA AND ALVEOLAR SOFT PART SARCOMA (OSCAR TRIAL, NCCH1510): A MULTICENTER, PHASE 2 CLINICAL TRIAL

Akira Kawai[2], *Tadaaki Nishikawa*[1], *Mamiko Kawasaki*[3], *Sawako Tomatsuri*[3], *Nobuko Okamura*[3], *Gakuto Ogawa*[3], *Akihiro Hirakawa*[4], *Taro Shibata*[3], *Kenichi Nakamura*[3], *Shigeki Kakunaga*[5], *Kenji Tamura*[1], *Masashi Ando*[6], *Toshifumi Ozaki*[7], *Takafumi Ueda*[5], *Kan Yonemori*[1]
[1]*Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, JAPAN;* [2]*Oncology and Rehabilitation Medicine, National Cancer Center Hospital, Tokyo, JAPAN;* [3]*National Cancer Center, Tokyo, JAPAN;* [4]*Tokyo Medical and Dental University, Tokyo, JAPAN;* [5]*Orthopaedic Surgery, National Hospital Organization Osaka National Hospital, Osaka, JAPAN;* [6]*Aichi Cancer Center, Aichi, JAPAN;* [7]*Orthopaedic Surgery, Okayama University, Okayama, JAPAN*

Paper #02 3464044

EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN ALVEOLAR SOFT PART SARCOMA: RESULTS FROM A RETROSPECTIVE WORLD-WIDE REGISTRY

Nadia Hindi[1], *Evan Rosenbaum*[2], *Piotr Rutkowski*[3], *Hans Gelderblom*[4], *Kjetil Boye*[5], *Clemence Henon*[6], *Bruno Vincenzi*[7], *Andres Redondo*[8], *Javier Martinez-Trufero*[9], *Claudia Valverde*[10], *Jose Antonio Lopez-Martin*[11], *Paulina Jagodzinska*[3], *Elizabeth Connolly*[12], *William D. Tap*[2], *Javier Martin-Broto*[1]
[1]*Medical Oncology, Hospital Universitario Virgen del Rocio, Instituto de Biomedicina de Sevilla (IBIS), Seville, SPAIN;* [2]*Memorial Sloan Kettering Cancer Center, New York, New York, UNITED STATES;* [3]*Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, POLAND;* [4]*Leiden University Medical Center, Leiden, NETHERLANDS;* [5]*Institute for Cancer Research, Oslo University Hospital, Department of Oncology, Oslo University Hospital, Oslo, NORWAY;* [6]*C. Henon, Medical Oncology, Institut de Cancérologie Gustave Roussy, Villejuif, FRANCE;* [7]*Medical Oncology, University Campus Bio-Medico, Rome, ITALY;* [8]*Medical Oncology, Hospital Universitario La Paz - IdiPAZ, Madrid, SPAIN;* [9]*Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza, SPAIN;* [10]*Medical Oncology, Hospital Universitario Vall d'Hebron, Barcelona, SPAIN;* [11]*Medical Oncology, Hospital Universitario 12 de Octubre,Translational Oncology Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, SPAIN;* [12]*Chris O Brien Lifehouse, Sydney, New South Wales, AUSTRALIA*

Paper #03 3462142

FINAL ANALYSIS OF THE PHASE 1 TRIAL OF NY-ESO-1-SPECIFIC T-CELL RECEPTOR (TCR) T-CELL THERAPY (LETETRESGENE AUTOLEUCEL; GSK3377794) IN PATIENTS (PTS) WITH ADVANCED SYNOVIAL SARCOMA (SS)

Sandra D'Angelo[1], *George Demetri*[2], *Brian A. Van Tine*[3], *Mihaela Druta*[4], *John Glod*[5], *Warren Chow*[6], *Naimish Pandya*[7], *Aisha Hasan*[7], *Victoria L. Chiou*[7], *Jenna Tress*[7], *Julie Edwards*[8], *Tim Young*[7], *Mary Woessner*[7], *Alexandra Gyurdieva*[7], *Stefan Zajic*[7], *Sophia Goodison*[7], *Dejka Araujo*[9]
[1]*Memorial Sloan Kettering Cancer Center, New York, New York, UNITED STATES;* [2]*Dana Farber Cancer Institute and Ludwig Center at Harvard, Boston, Massachusetts, UNITED STATES;* [3]*Washington University, St. Louis, Missouri, UNITED STATES;* [4]*H. Lee Moffitt Cancer Center, Tampa, Florida, UNITED STATES;* [5]*National Cancer Institute, Bethesda, Maryland, UNITED STATES;* [6]*City of Hope Comprehensive Cancer Center, Duarte, California, UNITED STATES;* [7]*GlaxoSmithKline, Collegeville, Pennsylvania, UNITED STATES;* [8]*GlaxoSmithKline, Stockley Park, Middlesex, UNITED KINGDOM;* [9]*University of Texas/MD Anderson Cancer Center, Houston, Texas, UNITED STATES*

Paper #04 3463188

DURABLE RESPONSES IN PATIENTS WITH SYNOVIAL SARCOMA IN THE PHASE I TRIAL OF ADP-A2M4 (MAGE-A4)

Brian A. Van Tine[1], *David S. Hong*[2], *Melissa L. Johnson*[6], *David A. Liebner*[3], *Kunle Odunsi*[4], *Trupti Trivedi*[8], *Quan Lin*[8], *Swethajit Biswas*[7], *Erica Elefant*[8], *Jean-Marc Navenot*[8], *Joana Senra*[7], *Zohar Wolchinsky*[7], *Robyn Broad*[7], *Gareth Betts*[7], *Natalie Bath*[7], *Will Spinner*[7], *Alex Tipping*[7], *Svetlana Fayngerts*[8], *Karen Miller*[7], *Amy Sun*[8], *Dennis Williams*[8], *Paula M. Fracasso*[8], *Elliott Norry*[8], *Marcus O. Butler*[5]

[1]*Washington University, St. Louis, St. Louis, Missouri, UNITED STATES;* [2]*The University of Texas, MD Anderson Cancer Center, Houston, Texas, UNITED STATES;* [3]*Ohio State University Medical Center, Columbus, Ohio, UNITED STATES;* [4]*Roswell Park Comprehensive Cancer Center, Buffalo, New York, UNITED STATES;* [5]*Princess Margaret Cancer Centre, Toronto, Ontario, CANADA;* [6]*Sarah Cannon Research Institute, Nashville, Tennessee, UNITED STATES;* [7]*Adaptimmune Ltd, Abingdon, Oxfordshire, UNITED KINGDOM;* [8]*Adaptimmune LLC, Philadelphia, Pennsylvania, UNITED STATES*

10:00 am - 10:30 am Morning Break

10:30 am - 11:30 am

– Special Awards Session –

YOUNG INVESTIGATOR AWARD WINNERS

Brittany Glassberg, BS
Shiv Verma, MD
Introduction by Program Chairs: **Stacchiotti, von Mehren, Schaefer**

Young Investigator Award 3464426

INCIDENCE OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MPNST) DEVELOPMENT IN PATIENTS WITH NF1 RECEIVING AND NOT RECEIVING MEDICAL THERAPIES DIRECTED AT PLEXIFORM NEUROFIBROMAS (PN)

Brittany Glassberg[1], *Andrea Gross*[1], *Eva Dombi*[1], *Andrea Baldwin*[1], *Trish Whitcomb*[1], *Ana Best*[1], *Amanda Carbonell*[1], *Kara Heisey*[1], *Janet Therrien*[1], *Oxana Kapustina*[1], *Brigitte C. Widemann*[1], *Hari Sankaran*[1]

[1]*Pediatric Oncology Branch, National Institutes of Health, Woodbury, New York, UNITED STATES*

Young Investigator Award 3465542

THE ASPSCR1-TFE3 TRANSCRIPTIONAL COMPLEX IN ALVEOLAR SOFT PART SARCOMAGENESIS

Shiv Verma[1]*; Amir Pozner*[1]*; Li Li*[1]*; Shuxin Wang*[2]*; Jared J. Barrott*[1]*; Sarmishta Kannan*[1]*; Jamie Yu*[3]*; Sydney L. Lambert*[1]*; Alexander Lazar*[4]*; Martin Hirst*[5]*; Torsten O. Nielsen*[3]*; Peter S. Shen*[2]*; Kevin B. Jones*[1]

[1]*Orthopaedics and Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, UNITED STATES;* [2]*Department of Biochemistry, University of Utah, Salt Lake City, Utah, UNITED STATES;* [3]*Department of Pathology, University of British Columbia, Vancouver, British Columbia, CANADA;* [4]*Department of Pathology, MD Anderson Cancer Center, Houston, Texas, UNITED STATES;* [5]*Genome Sciences Center, University of British Columbia, Vancouver, British Columbia, CANADA*

LIDDY SHRIVER EARLY RESEARCH AWARD WINNER

Professor Nicolo Riggi
Introduction by Chair: **David Thomas**

BASIC SCIENCE SARCOMA RESEARCH AWARD WINNERS

David Kirsch
Benjamin Nacev
Isidro Cortes-Ciriano
Introduction by Chair: **Lee Helman**

11:30 am - 12:30 pm

– Session 3 –

NATIONAL LEIOMYOSARCOMA FOUNDATION RESEARCH GRANT

Chair: **Seth Pollack**

LEIOMYOSARCOMA AND UNDIFFERENTIATED PLEOMORPHIC SARCOMA

Chair: **Suzanne George**
Discussant: **Dirk Strauss**
Panelists: **Matt van de Rijn**, **Paolo A. Dei Tos**, **Robin Jones**
Presenters: **Sant P. Chawla**, **Nathaniel Anderson**, **Nicolas A. Devaud**, **Nathan D. Seligson**

Paper #05 3465673

UPDATED PHASE I STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RIVOCERANIB (APATINIB) AND NIVOLUMAB IN PATIENTS WITH UNRESECTABLE OR METASTATIC CANCER

Sant P. Chawla[1], *Victoria Chua-Alcala*[1], *Steven M. Wong*[1], *Doris Quon*[1], *Ania M. Moradkhani*[1], *Kelly Wang*[1], *Ish Bhuiyan*[1], *Olivia Pelenghian*[1], *Sandon Scott*[1], *Natalie Krkyan*[1], *Kitty Zheng*[1], *Steven Norton*[2], *Kehua Wu*[2], *Ted M. Kim*[1], *Erlinda M. Gordon*[1]
[1]*Sarcoma Oncology Center, Santa Monica, California, UNITED STATES;* [2]*Elevartherapeutics,Inc., Salt Lake City, Utah, UNITED STATES*

Paper #06 3463196

LINEAGE-DEFINED LEIOMYOSARCOMA SUBTYPES EMERGE YEARS BEFORE DIAGNOSIS, DETERMINING PATIENT SURVIVAL

Nathaniel Anderson[1], *Yael Babichev*[2], *Fabio Fuligni*[1], *Federico Comitani*[1], *Mehdi Layeghifard*[1], *Rosemarie Venier*[2], *Anant Maheshwari*[1], *Sheena Guram*[2], *Claire Wunker*[2], *J. Drew Thompson*[1], *Marcus Bernadini*[3], *Jay Wunder*[2], *Irene Andrulis*[2], *Peter Ferguson*[4], *Albiruni Abdul Razak*[3], *Carol J. Swallow*[2], *Rima Al-Awar*[5], *Richard Marcellus*[5], *Marjan Rouzbahman*[3], *Daniel Durocher*[2], *Ludmil Alexandrov*[6], *Brendan Dickson*[2], *Rebecca Gladdy*[2], *Adam Shlien*[1]
[1]*Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Ontario, CANADA;* [2]*Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, CANADA;* [3]*University Health Network, Toronto, Ontario, CANADA;* [4]*University Musculoskeletal Oncology Unit, Mount Sinai Hospital, Toronto, Ontario, CANADA;* [5]*Ontario Institute for Cancer Research, Toronto, Ontario, CANADA;* [6]*University of California San Diego, San Diego, California, UNITED STATES*

Paper #07 3464097

IS SITE OF ORIGIN (IVC VS. NON-IVC) PROGNOSTIC FOLLOWING RESECTION OF PRIMARY RETROPERITONEAL LEIOMYOSARCOMA (RP LMS)? COMBINED EXPERIENCE OF TWO SARCOMA REFERRAL CENTRES

Nicolas A. Devaud[1], *Deanna Ng*[1], *Harini Suraweera*[1], *Abha A. Gupta*[2], *Albiruni Razak*[2], *Peter Chung*[3], *Savtaj Brar*[1], *Thomas Lindsay*[1], *Rebecca Gladdy*[1], *Ian McGilvray*[1], *Claudia Sangalli*[5], *Roberta Sanfilippo*[4], *Silvia Stacchiotti*[4], *Dario Callegaro*[6], *Marco Fiore*[6], *Alessandro Gronchi*[6], *Carol J. Swallow*[1]
[1]*Surgery, University of Toronto, Toronto, Ontario, CANADA;* [2]*Medical Oncology, University of Toronto, Toronto, Ontario, CANADA;* [3]*Radiation Oncology, University of Toronto, Toronto, Ontario, CANADA;* [4]*Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Lombardia, ITALY;* [5]*Radiation Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Lombardia, ITALY;* [6]*Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Lombardia, ITALY*

Paper #08 3457194

HOMOLOGOUS RECOMBINATION DNA REPAIR AND LOSS OF HETEROZYGOSITY IN LEIOMYOSARCOMA

Nathan D. Seligson[1], *Sherri Z. Millis*[3], *Dexter Jin*[3], *Nicholas Grosenbacher*[2], *Monica P. Bennett*[1], *Alexander M. Litvintchouk*[1], *Colin M. Stets*[2], *Julia A. Elvin*[3], *John L. Hays*[2], *James Chen*[2]
[1]*University of Florida, Jacksonville, Florida, UNITED STATES;* [2]*Ohio State University, Columbus, Ohio, UNITED STATES;* [3]*Foundation Medicine Inc, Cambridge, Massachusetts, UNITED STATES*

12:30 pm - 1:30 pm — **– Session 4 –**

OSTEOSARCOMA AND PEDIATRIC BONE SARCOMAS

Chair: **Maureen O'Sullivan**
Discussant: **Lor Randall**
Panelists: **Emanuela Palmerini**, **Petur Nielsen**, **Kurt Weiss**
Presenters: **Jong Min Lee**, **Kelly Bailey**, **Reid Davison**, **Jovana Pavisic**

Paper #09 3437417

A COMPARISON OF ONCOLOGICAL AND SURGICAL OUTCOMES IN ENDOPROSTHETIC RECONSTRUCTION VERSUS ROTATIONPLASTY FOR PAEDIATRIC LOWER EXTREMITY BONE SARCOMA

Jong Min Lee[2], *Jonathan R. Perera*[1], *Eliane R. Trottier*[2], *Sevan Hopyan*[2], *Kim Tsoi*[1]
[1]*Orthopaedic Oncology, Mount Sinai Hospital, Amersham, Buckinghamshire, UNITED KINGDOM;* [2]*Paediatric Orthopaedics, SickKids, Toronto, Ontario, CANADA*

Thursday, 19 November, 2020

Paper #10 3464085

EXPRESSION PROFILING AND SPATIAL LOCALIZATION OF CD45+ LEUKOCYTES INFILTRATING PRIMARY AND RELAPSED BONE SARCOMAS

*Anthony Cillo[2], Elina Mukherjee[3], Sayali Onkar[2], Kurt R. Weiss[4], Melissa A. Burgess[5], Tanya Heim[4], Dario Vignali[2], Tullia Bruno[2], **Kelly Bailey**[1]*

[1]Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, UNITED STATES; [2]Immunology, Univeristy of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, UNITED STATES; [3]Pediatrics, University of Pittsburgh, Pittsburgh, Pennsylvania, UNITED STATES; [4]Orthopaedic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, UNITED STATES; [5]Medicine, University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, Pennsylvania, UNITED STATES

Paper #11 3446540

PULMONARY MICRONODULES LESS THAN 5 MM DETECTED ON CT AT PRESENTATION IN PATIENTS WITH OSTEOSARCOMA DO NOT EFFECT 5 YEAR OVERALL SURVIVAL

Reid Davison[1], *Fadi Hamati[1], Paul Kent[1]*

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Paper #12 3461610

TARGETING MASTER REGULATOR DEPENDENCIES IN PEDIATRIC OSTEOSARCOMA

Jovana Pavisic[1], *Katherine Janeway[2], Andrew Kung[3], Filemon Dela Cruz[3], Alejandro Sweet-Cordero[5], Inge Behroozfard[5], Stanley Leung[5], Alex Lee[5], Darrell Yamashiro[1], Julia Glade Bender[3], Andrea Califano[4]*

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1:30 pm - 2:30 pm

MEET THE EXPERTS
Multidisciplinary Discussion of Clinical Cases

Room 1:	Room 2:	Room 3:
GIST	**Bone Sarcomas**	**Soft Tissue Sarcomas**
Moderator: **William Tap**	Moderator & Presenter: **Anna Maria Frezza**	Moderator: **Rick Haas**
Presenter: **Maria Abbondanza Pantaleo**	Panelists: **Josh Sommer** **Abha Gupta** **Hans Gelderblom** **Sandra Strauss** **Jay Wunder** **Thomas DeLaney** **Paolo A. Dei Tos** **Kannan Rajesparan**	Presenter: **Armelle Dufresne**
Panelists: **Sara Rothschild** **George Demetri** **Tom Wei-Wu Chen** **Paolo Casali** **Piotr Rutkowski** **Aisha Miah** **Eva Wardelmann**		Panelists: **Roger Wilson** **Jean Yves Blay** **Andrew Wagner** **Claudia Valverde Morales** **Alessandro Gronchi** **Elizabeth Baldini** **Christopher Fletcher**

2:30 pm - 3:30 pm CTOS Executive Committee Meeting

Thursday, 19 November, 2020

3:00 pm - 4:30 pm	– Symposium – **THE CASE FOR CHALLENGING CONVENTIONAL CARE IN TENOSYNOVIAL GIANT CELL TUMOR: INSIGHTS ON INTEGRATING TARGETED THERAPY INTO MULTIMODAL MANAGEMENT**

Friday, 20 November, 2020

8:00 am - 9:00 am — **– Session 5 –**

"WHAT IS NEW IN SARCOMA PATHOLOGY AND MOLECULAR DIAGNOSTICS"

Cristina Antonescu

9:00 am - 10:00 am — **– Session 6 –**

CHONDROSARCOMA, CHORDOMA, AND OTHER BONE TUMORS

Chair: **Judith Bovée**
Discussant: **David Kirsch**
Panelists: **Elizabeth Baldini**, **Javier Martin-Broto**, **Rick Haas**
Presenters: **Sanne Venneker**, **Ivar Hompland**, **Thomas F. DeLaney**, **Sant P. Chawla**

Paper #13 3465391

BEYOND THE INFLUENCE OF IDH MUTATIONS: EXPLORING EPIGENETIC VULNERABILITIES IN CHONDROSARCOMA

Sanne Venneker[1], *Alwine B. Kruisselbrink*[1], *Zuzanna Baranski*[2], *Ieva Palubeckaite*[1], *Inge H. Briaire-de Bruijn*[1], *Jan Oosting*[1], *Pim J. French*[3], *Erik Danen*[2], *Judith V. Bovee*[1]
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Paper #14 3442269

OUTCOME IN DEDIFFERENTIATED CHONDROSAROMA FOR PATIENTS TREATED WITH MULTIMODAL THERAPY: RESULTS FROM THE EURO-B.O.S.S STUDY

Ivar Hompland[1], *Stefano Ferrari*[2], *Stefan Bielack*[3], *Emanuela Palmerini*[2], *Kirsten S. Hall*[1], *Davide M. Donati*[2], *Elisabetta Setola*[2], *Virginia Ferraresi*[4], *Rossella Bertulli*[9], *Alessandro Comandone*[5], *Pierro Picci*[1], *Stefanie Hecker-Nolting*[3], *Claudia Blattmann*[3], *Leo Kager*[7], *Thomas Kühne*[6], *Peter Reichardt*[8], *Sigbjørn Smeland*[1]
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Paper #15 3461741

DEFINITIVE HIGH-DOSE, PROTON-BASED RADIATION FOR UNRESECTED MOBILE SPINE AND SACRAL CHORDOMAS

Thomas F. DeLaney[1], *Norbert J. Liebsch*[1], *Saveli Goldberg*[1], *Walter H. Banfield*[2], *Myrsini Ioakeim-Ioannidou*[1], *Soha Ahmed*[3], *Joseph H. Schwab*[4], *Francis J. Hornicek*[7], *Gregory M. Cote*[5], *John H. Shin*[6], *Edwin Choy*[5], *Yen-Lin E. Chen*[1]
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Paper #16 3463234

RESULTS FROM THE CHONDROSARCOMA PHASE 1 STUDY EXPANSION COHORT OF THE TETRAVALENT DEATH RECEPTOR 5 AGONIST INBRX-109

Sant P. Chawla[1], *Nehal Lakhani*[4], *Anthony Tolcher*[5], *Christopher Lieu*[3], *Breelyn A. Wilky*[3], *Klaus W. Wagner*[2], *Analeah Heidt*[2], *Brendan Eckelman*[2], *Quinn Deveraux*[2], *James Kalabus*[2], *Anthony P. Conley*[6], *Vivek Subbiah*[6]
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10:00 am - 10:30 am Morning Break

10:30 am - 11:30 am – Session 7 –

LIPOSARCOMA

Chair: **Mark Dickson**
Discussant: **Carol Swallow**
Panelists: **Neeta Somaiah**, **Alessandro Gronchi**
Presenters: **Dario Callegaro**, **Jonathan R. Perera**, **Jules Lansu**, **Mrinal Gounder**, **Marco Fiore**

Paper #17 3464763

PREOPERATIVE RADIOTHERAPY IN PATIENTS WITH PRIMARY RETROPERITONEAL SARCOMA (RPS): TRIAL (STRASS) VS OFF-TRIAL (STREXIT) RESULTS

Dario Callegaro[1], *Chandrajit Raut*[12], *Ajayi Taiwo*[2], *Dirk Strauss*[3], *Sylvie Bonvalot*[4], *Deanna Ng*[5], *Eberhard Stoeckle*[6], *Mark Fairweather*[12], *Piotr Rutkowski*[7], *Winan J. van Houdt*[8], *Hans Gelderblom*[9], *Claudia Sangalli*[13], *Andrew Hayes*[3], *Charles Honoré*[10], *Rebecca Gladdy*[5], *Magali Fau*[6], *Rick L. Haas*[11], *Dmitri Tzanis*[4], *Aisha B. Miah*[14], *Peter Chung*[15], *Elizabeth H. Baldini*[16], *Sandrine Marreaud*[2], *Saskia Litière*[2], *Carol J. Swallow*[5], *Alessandro Gronchi*[1]
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Paper #18 3437448

INTERMUSCULAR MYXOID LIPOSARCOMA CAN BE MANAGED BY MARGINAL SURGICAL RESECTION FOLLOWING NEOADJUVANT RADIOTHERAPY

Jonathan R. Perera[1], *Ahmed Aoude*[1], *Izuchuwu Ibe*[1], *Anthony Griffin*[1], *Peter Ferguson*[1], *Jay Wunder*[1], *Kim Tsoi*[1]
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Paper #19 3437081

DOSE REDUCTION OF PREOPERATIVE RADIOTHERAPY FOR MYXOID LIPOSARCOMA (DOREMY): A PROSPECTIVE, MULTICENTER, SINGLE-ARM, PHASE 2 TRIAL

Jules Lansu[1], *Judith V. Bovee*[2], *Pètra Braam*[3], *Hester van Boven*[4], *Uta Flucke*[3], *Han Bonenkamp*[3], *Aisha B. Miah*[5], *Shane H. Zaidi*[5], *Khin Thway*[5], *Øyvind S. Bruland*[6], *Elizabeth H. Baldini*[7], *Nina L. Jebsen*[8], *Astrid N. Scholten*[1], *Piet L. van den Ende*[9], *Augustinus D. Krol*[2], *Fred Ubbels*[10], *Jos A. van der Hage*[2], *Erik van Werkhoven*[4], *Houke M. Klomp*[4], *Winette T. van der Graaf*[4], *Frits van Coevorden*[4], *Yvonne Schrage*[4], *Winan J. van Houdt*[4], *Rick L. Haas*[1]
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Paper #20 3461475

A PHASE 2/3, RANDOMIZED, DOUBLE BLIND, CROSS-OVER, STUDY OF SELINEXOR VERSUS PLACEBO IN ADVANCED UNRESECTABLE DEDIFFERENTIATED LIPOSARCOMA (DDLS)

Mrinal Gounder[1], *Albiruni Abdul Razak*[2], *Neeta Somaiah*[3], *Javier Martin-Broto*[4], *Scott Schuetze*[5], *Giovanni Grignani*[6], *Sant P. Chawla*[7], *Bartosz Chmielowski*[8], *Bruno Vincenzi*[9], *Silvia Stacchiotti*[10], *Andrew J. Wagner*[11], *Axel Le Cesne*[12], *Richard F. Riedel*[13], *Robin L. Jones*[14], *Kristen Ganjoo*[15], *Xavier Garcia del Muro*[16], *Melissa A. Burgess*[17], *Dayana Michel*[18], *Hongwei Wang*[18], *Jatin J. Shah*[18], *Steven Attia*[19]
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Paper #21 3447775

NEUTROPHIL-TO-LYMPHOCYTE RATIO IS A PROGNOSTIC FACTOR REGARDLESS PREOPERATIVE TREATMENTS IN PRIMARY RETROPERITONEAL SARCOMA

Marco Fiore[1], *Sandro Pasquali*[1], *Daniele Morelli*[2], *Giuseppe Cuomo*[2], *Marta Barisella*[3], *Claudia Sangalli*[4], *Alessandro Gronchi*[1]
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11:30 am - 12:30 pm — – Session 8 –

GIST

Chair: **Cesar Serrano**
Discussant: **Ron deMatteo**
Panelists: **Chandrajit Raut**, **Piotr Rutkowski**
Presenters: **Jason Sicklick**, **Lorenzo D'Ambrosio**, **Jonathan Trent**, **Suzanne George**, **Sebastian Bauer**

Paper #22 3462544

HUMAN SUCCINATE DEHYDROGENASE-DEFICIENT GASTROINTESTINAL STROMAL TUMORS ARE SENSITIVE TO TEMOZOLOMIDE VIA INDUCTION OF ER STRESS AND DNA DAMAGE

*Mayra Yebra[1], Avi Kumar[2], Adam Burgoyne[3], Chih-Min Tang[1], Hyunho Yoon[1], Sudeep Banerjee[4], Joseph Aguilera[1], Thekla Cordes[1], Vipul Sheth[5], Sangkyu Noh[1], Rowan Ustoy[1], Sunil Advani[1], Christopher Corless[7], Michael Heinrich[6], Razelle Kurzrock[1], Scott M. Lippman[1], Paul T. Fanta[1], Olivier Harismendy[1], Christian Metallo[1], **Jason K. Sicklick**[1]*
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Paper #23 3465722

ASSESSMENT OF A GUIDELINE-BASED FOLLOW-UP STRATEGY AFTER COMPLETE SURGERY IN PATIENTS AFFECTED BY GASTROINTESTINAL STROMAL TUMOR (GIST) WITH LOW-RISK OF RECURRENCE

Lorenzo D'Ambrosio[1], *Elena Fumagalli*[2], *Margherita Nannini*[3], *Tommaso Martino De Pas*[4], *Bruno Vincenzi*[5], *Francesca Ligorio*[2], *Elisabetta Pennacchioli*[6], *Andrea Mogavero*[1], *Antonella Brunello*[7], *Fabio Conforti*[4], *Danila Comandini*[8], *Giulia Manessi*[1], *Silvia Gasperoni*[9], *Virginia Ferraresi*[10], *Giuseppe Badalamenti*[11], *Sandra Aliberti*[1], *Marco Fiore*[12], *Maria Pantaleo*[3], *Giovanni Grignani*[1]

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Paper #24 3458521

THE POTENT AND SELECTIVE KIT INHIBITOR PLX9486 DOSED IN COMBINATION WITH SUNITINIB DEMONSTRATES PROMISING PROGRESSION FREE SURVIVAL (PFS) IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR (GIST): FINAL RESULTS OF A PHASE 1/2 STUDY

Jonathan Trent[1], *William D. Tap*[2], *Rashmi Chugh*[3], *Gabriel Tinoco*[4], *Athanasios Tsiatis*[5], *Paul Severson*[5], *Kerry Inokuchi*[5], *Chao Zhang*[5], *Glenn Michelson*[7], *Andrew J. Wagner*[6]

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Paper #25 3463167

RIPRETINIB INTRA-PATIENT DOSE ESCALATION FOLLOWING DISEASE PROGRESSION PROVIDES CLINICALLY MEANINGFUL PROGRESSION-FREE SURVIVAL IN GASTROINTESTINAL STROMAL TUMOR IN PHASE 1 STUDY

Suzanne George[1], *Ping Chi*[2], *Michael Heinrich*[3], *Margaret von Mehren*[4], *Robin L. Jones*[5], *Kristen Ganjoo*[6], *Jonathan Trent*[7], *Hans Gelderblom*[8], *Albiruni Abdul Razak*[9], *Michael Gordon*[10], *Neeta Somaiah*[11], *Julia Jennings*[12], *Kelvin Shi*[12], *Rodrigo Ruiz-Soto*[12], *Filip Janku*[13]

[1]*Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, UNITED STATES;* [2]*Human Oncology and Pathogenesis Program & Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, UNITED STATES;* [3]*Hematology/Medical Oncology, OHSU Knight Cancer Institute, Portland, Oregon, UNITED STATES;* [4]*Hematology Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, UNITED STATES;* [5]*Royal Marsden and Institute of Cancer Research, London, UNITED KINGDOM;* [6]*Medical Oncology, Stanford University, Stanford, California, UNITED STATES;* [7]*Medical Oncology, Sylvester Comprehensive Cancer Center/University of Miami, Miami, Florida, UNITED STATES;* [8]*Medical Oncology, Leiden University Medical Center, Leiden, NETHERLANDS;* [9]*Toronto Sarcoma Program, Princess Margaret Cancer Centre, Toronto, Ontario, CANADA;* [10]*HonorHealth Research Institute, Scottsdale, Arizona, UNITED STATES;* [11]*Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, UNITED STATES;* [12]*Deciphera Pharmaceuticals, LLC, Waltham, Massachusetts, UNITED STATES;* [13]*Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas, UNITED STATES*

Paper #26 3443599

CHARACTERIZATION OF THE EXTENSIVE HETEROGENEITY OF KIT/PDGFRA MUTATIONS IN PATIENTS WITH FOURTH-LINE ADVANCED GASTROINTESTINAL STROMAL TUMOR: GENOMIC ANALYSIS OF THE PHASE 3 INVICTUS STUDY

Sebastian Bauer[1], *Patrick Schöffski*[2], *Michael Heinrich*[3], *Suzanne George*[4], *John Zalcberg*[5], *Hans Gelderblom*[6], *César Serrano*[7], *Robin L. Jones*[8], *Steven Attia*[9], *Gina D'amato*[10], *Ping Chi*[11], *Peter Reichardt*[12], *Julie Meade*[13], *Vienna L. Reichert*[13], *Ying Su*[13], *Rodrigo Ruiz-Soto*[13], *Jean-Yves Blay*[14], *Margaret von Mehren*[15]

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12:30 pm - 1:30 pm	**HERMAN SUIT LECTURE – GENETICS, GENOMICS AND SARCOMAS** **David Thomas**
1:30 pm - 2:30 pm	**VIRTUAL GET-TOGETHER**
2:30 pm - 3:30 pm	CTOS Board of Directors Meeting
3:00 pm - 4:00 pm	– Symposium – **PERSONALIZING AND PROLONGING CARE IN GIST: EXPERT GUIDANCE ON INTEGRATING NEW TKI STRATEGIES**

Saturday, 21 November, 2020

8:00 am - 9:00 am

– Session 9 –

EPIGENETICALLY DRIVEN SARCOMAS

Presenter: **Cigall Kadoch**

9:00 am - 10:00 am

– Session 10 –

ADVANCES IN ANGIOSARCOMA, PECOMA, AND CLEAR CELL SARCOMA

Chair: **Vinod Ravi**
Discussant: **William Tap**
Panelists: **Winette van der Graaf**, **Cristina Antonescu**, **Jayesh Desai**
Presenters: **Andrea Espejo-Freire**, **Jessica Burns**, **Andrew J. Wagner**, **Ben Ozenberger**

Paper #27 3460221

GENOMIC LANDSCAPE OF ANGIOSARCOMA: A TARGETED AND IMMUNOTHERAPY BIOMARKER ANALYSIS OF 143 PATIENTS

Andrea Espejo-Freire[1], *Andrew Elliott*[2], *Yamac Akgun*[1], *Philippos A. Costa*[1], *Maryam Alasfour*[1], *Andrew Rosenberg*[1], *Julio Diaz-Perez*[1], *Gina D'amato*[1], *Ty K. Subhawong*[1], *Junaid Arshad*[1], *W. Michael Korn*[2], *Don Dizon*[3], *Margaret von Mehren*[4], *Moh'd Khushman*[5], *Atif Hussein*[6], *Kirsten Leu*[7], *Jonathan Trent*[1]
[1]*University of Miami Sylvester Comprehensive Cancer Center, Jackson Memorial Hospital, Miami, Florida, UNITED STATES;* [2]*Caris Life Sciences, Irving, Texas, UNITED STATES;* [3]*Brown University Lifespan Cancer Institute, Providence, Rhode Island, UNITED STATES;* [4]*Fox Chase Cancer Center, Philadelphia, Pennsylvania, UNITED STATES;* [5]*University of South Alabama Mitchell Cancer Institute, Mobile, Alabama, UNITED STATES;* [6]*Memorial Cancer Institute, Hollywood, Florida, UNITED STATES;* [7]*Nebraska Cancer Specialists, Omaha, Nebraska, UNITED STATES*

Paper #28 3464567

THE PROTEOME LANDSCAPE OF SOFT TISSUE SARCOMAS DEFINES TWO FUNCTIONAL SUBGROUPS OF ANGIOSARCOMAS WITH DISTINCT SURVIVAL OUTCOMES

Jessica Burns[1], *Lukas Krasny*[1], *Christopher Wilding*[1], *Maggie Cheang*[1], *Robin L. Jones*[2], *Paul Huang*[1]
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Paper #29 3463014

LONG-TERM FOLLOW-UP FROM AMPECT, AN OPEN-LABEL PHASE 2 REGISTRATION TRIAL OF NAB-SIROLIMUS FOR PATIENTS WITH ADVANCED MALIGNANT PERIVASCULAR EPITHELIOID CELL TUMORS (PECOMA)

Andrew J. Wagner[1], *Vinod Ravi*[2], *Richard F. Riedel*[3], *Kristen Ganjoo*[5], *Brian A. Van Tine*[6], *Rashmi Chugh*[7], *Lee D. Cranmer*[8], *Erlinda M. Gordon*[9], *Jason L. Hornick*[10], *Heng Du*[10], *Berta Grigorian*[4], *Anita N. Schmid*[4], *Shihe Hou*[4], *Katherine Harris*[4], *David Kwiatkowski*[10], *Neil Desai*[4], *Mark Dickson*[11]
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Paper #30 3465453

BEYOND THE FUSION: THE CLEAR CELL SARCOMA FUNCTIONAL GENOME

*Emanuele Panza[2], **Ben Ozenberger**[1], Krystal Straessler[3], Jared J. Barrott[4], Anne M. Boulet[5], Clint Mason[6], Alexander Lazar[7], Mario R. Capecchi[5], Kevin B. Jones[1]*

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10:00 am - 10:30 am Morning Break

10:30 am - 11:30 am **NINA AXELRAD LECTURE – EVOLUTION OF DOGMAS IN SARCOMA SURGERY**

Sylvie Bonvalot

11:30 am - 12:30 pm — **– Session 11 –**

RHABDOMYOSARCOMA AND EWING SARCOMA

Chair: **Kevin Jones**
Discussant: **Katherine Janeway**
Panelists: **Richard Womer**, **Rashmi Chugh**
Presenters: **Christine M. Heske**, **Wendy Allen-Rhoades**, **Margaret B. Nagel**, **Megann Boone**, **Joseph A. Ludwig**

Paper #31 3443006

SURVIVAL OUTCOMES OF PATIENTS WITH LOCALIZED FOXO1 FUSION POSITIVE RHABDOMYOSARCOMA TREATED ON RECENT CHILDREN'S ONCOLOGY GROUP CLINICAL TRIALS

Christine M. Heske[1], *Yueh-Yun Chi*[2], *Rajkumar Venkatramani*[3], *Minjie Li*[2], *Michael Arnold*[4], *Roshni Dasgupta*[5], *Susan M. Hiniker*[6], *Douglas S. Hawkins*[7], *Leo Mascarenhas*[8]
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Paper #32 3461602

ALVEOLAR RHABDOMYOSARCOMA HAS SUPERIOR CLINICAL RESPONSE RATES TO VINORELBINE COMPARED TO EMBRYONAL RHABDOMYOSARCOMA IN PATIENTS WITH REFRACTORY OR RELAPSED DISEASE

Wendy Allen-Rhoades[1], *Philip Lupo*[1], *Michael Scheurer*[1], *Yueh-Yun Chi*[2], *John Kuttesch*[3], *William H. Meyer*[4], *Rajkumar Venkatramani*[1], *Leo Mascarenhas*[2]
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Paper #33 3457806

THE ROLE OF DLK1 IN FUSION-NEGATIVE RHABDOMYOSARCOMA

Margaret B. Nagel[1], *Matthew R. Garcia*[1], *Mark E. Hatley*[1]
[1]*St Jude Children's Research Hospital, Memphis, Tennessee, UNITED STATES*

Paper #34 3435189

STRUCTURE-FUNCTION MAPPING REVEALS NOVEL REGION OF FLI CRITICAL FOR EWS/FLI ACTIVITY IN EWING SARCOMA

Megann Boone[1], *Cenny Taslim*[1], *Julia Selich-Anderson*[1], *Jesse Crow*[1], *Emily R. Theisen*[1], *Iftekhar Showpnil*[1], *Stephen Lessnick*[1]
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Paper #35 3464969

TK216 PHASE 1 STUDY IN METASTATIC, RELAPSED/REFRACTORY EWING SARCOMA

Joseph A. Ludwig[2], *Noah Federman*[4], *Peter Anderson*[10], *Margaret Macy*[3], *Lara E. Davis*[7], *Richard F. Riedel*[5], *Najat C. Daw*[2], *Jodi Muscal*[8], *Ravin Ratan*[2], *Jeffrey Toretsky*[6], *Xen Ianopulos*[1], *Frank Hsu*[1], *James Breitmeyer*[1], *Paul Meyers*[9]
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12:30 pm - 1:30 pm — Session 12 –

LOCALLY AGGRESSIVE MESENCHYMAL TUMORS: DESMOID TUMOR, DIFFUSE-TYPE GIANT CELL TUMOR

Chair: **Palma Dileo**
Discussant: **Winan Van Houdt**
Panelists: **Alexander Lazar**, **Bernd Kasper**, **Jay Wunder**
Presenters: **Javier Martin-Broto**, **Michael J. Nathenson**, **Albiruni Abdul Razak**

Lecture: **RECENT UPDATES IN LOCALLY AGGRESSIVE MESENCHYMAL TUMORS: DESMOID TUMOR, DIFFUSE-TYPE GIANT CELL TUMOR**

Mrinal Gounder

Paper #36 3465367

WEEKLY NAB-PACLITAXEL FOR PROGRESSIVE OR SYMPTHOMATIC DESMOID TUMORS: A MULTICENTER SINGLE ARM PHASE II TRIAL FROM THE SPANISH GROUP FOR RESEARCH ON SARCOMA (GEIS)

Javier Martin-Broto[1], *Nadia Hindi*[1], *Andres Redondo*[2], *Jose Manuel Morales*[3], *David Marcilla*[4], *Claudia Valverde*[5], *Pablo Luna*[6], *Robert D. Beveridge*[7], *Javier Martinez-Trufero*[8], *Jose Antonio Lopez-Martin*[9], *Virginia Martinez*[2], *Antonio Gutierrez*[10], *Antonio Lopez-Pousa*[11]
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Paper #37 3459474

ASSOCIATION OF CTNNB1 MUTATION SUBTYPES WITH RESPONSE TO SYSTEMIC THERAPY IN PATIENTS WITH DESMOID TUMORS: A MULTI-INSTITUTIONAL RETROSPECTIVE STUDY

Michael J. Nathenson[1], *Neeta Somaiah*[2], *Robert Hsu*[3], *Peter DeMaria*[3], *Heath Catoe*[3], *Karan Malik*[1], *Christy Harris*[1], *Ty K. Subhawong*[4], *Behrang Amini*[5], *Jyothi P. Jagannathan*[6], *Marta Braschi-Amirfarzan*[6], *Kevin Sweet*[4], *Katharina Feister*[4], *Junxiao Hu*[7], *Jamie Sheren*[8], *Andrew Rosenberg*[9], *Alexander Lazar*[10], *Ravin Ratan*[2], *Vinod Ravi*[2], *Shreyaskumar Patel*[2], *Robert Maki*[12], *Pasquale Benedetto*[3], *Jonathan Cohen*[3], *Jonathan Trent*[3], *Breelyn A. Wilky*[11]
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Paper #38 3461713

PHASE 1 DOSE-ESCALATION STUDY OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF DCC-3014 IN ADVANCED SOLID TUMORS AND TENOSYNOVIAL GIANT CELL TUMOR (TGCT)

Albiruni Abdul Razak[1], *Breelyn A. Wilky*[2], *Jacqueline Vuky*[3], *Lara E. Davis*[3], *Todd Bauer*[4], *Hans Gelderblom*[5], *Mary Michenzie*[6], *Maitreyi Sharma*[6], *Rodrigo Ruiz-Soto*[6], *Matthew L. Sherman*[6], *William D. Tap*[7]
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1:30 pm - 2:00 pm **CLOSING REMARKS**

President: **Kirsten Sundby Hall**
Program Chairs: **Silvia Stacchiotti**, **Margaret von Mehren**, **Inga-Marie Schaefer**

2:00 pm - 3:00 pm CTOS Members' Business Meeting

9:00 am - 10:00 am – Session 2 –

IMMUNOTHERAPY IN SARCOMA: ALVEOLAR SOFT PART SARCOMA, CLEAR CELL SARCOMA, SYNOVIAL SARCOMA

Paper #01 3421748

EFFICACY AND SAFETY OF NIVOLUMAB MONOTHERAPY IN PATIENTS WITH UNRESECTABLE CLEAR CELL SARCOMA AND ALVEOLAR SOFT PART SARCOMA (OSCAR TRIAL, NCCH1510): A MULTICENTER, PHASE 2 CLINICAL TRIAL

Akira Kawai[2], *Tadaaki Nishikawa*[1], *Mamiko Kawasaki*[3], *Sawako Tomatsuri*[3], *Nobuko Okamura*[3], *Gakuto Ogawa*[3], *Akihiro Hirakawa*[4], *Taro Shibata*[3], *Kenichi Nakamura*[3], *Shigeki Kakunaga*[5], *Kenji Tamura*[1], *Masashi Ando*[6], *Toshifumi Ozaki*[7], *Takafumi Ueda*[5], *Kan Yonemori*[1]

[1]*Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, JAPAN;* [2]*Oncology and Rehabilitation Medicine, National Cancer Center Hospital, Tokyo, JAPAN;* [3]*National Cancer Center, Tokyo, JAPAN;* [4]*Tokyo Medical and Dental University, Tokyo, JAPAN;* [5]*Orthopaedic Surgery, National Hospital Organization Osaka National Hospital, Osaka, JAPAN;* [6]*Aichi Cancer Center, Aichi, JAPAN;* [7]*Orthopaedic Surgery, Okayama University, Okayama, JAPAN*

Objective: Clear cell sarcoma (CCS) and alveolar soft part sarcoma (ASPS) are rare histology of soft tissue sarcomas, also known as the microphthalmia family of transcription factor (MITF)-associated tumors. These sarcomas have been considered insensitive to chemotherapy, however MITF-associated tumors have similar immunoreactivity to melanoma and efficacy of immune checkpoint inhibitor for ASPS has been reported. Therefore, we conducted a clinical trial to assess efficacy of nivolumab monotherapy for CCS and ASPS.

Methods: In this single arm, phase 2 trial, patients were enrolled with unresectable CCS and ASPS from November 2016 to January 2018, from four institutions in Japan. Patients received nivolumab 240 mg every two weeks until disease progression occurred or untolerable toxicity appeared. The primary endpoint was response rate (central review), and the secondary endpoints were response rate (site review), progression-free survival (PFS), overall survival (OS) and incidence of adverse events. The trial design was based on the Bayesian interim monitoring strategy that we specify the minimum and maximum numbers of enrolled patients during the enrollment period and the prior distributions of response rates before beginning the trial. Under these parameter settings with a prespecified threshold and expected response rate of 5% and 30%, we obtain the adaptive decision rule, i.e. the minimum number of responders needed for the positive conclusion of the efficacy of nivolumab for each sample size.

Results: 11 patients with unresectable CCS, 14 patients with unresectable ASPS were enrolled. One patient considered to be CCS was excluded for efficacy analysis by histological incompatibility. Efficacy was analyzed on 25 patients with CCS and ASPS, safety was analyzed on 26 patients. The minimum number of responses needed for positive conclusion of efficacy of nivolumab for 25 patients was four, but only one patient (4.0%) with ASPS had partial response (PR) on central review. Stable disease (SD) was 60% (15/25), progression disease (PD) was 32% (8/25) and complete response (CR) was 0% on central review. On the other hand, the number of partial response (PR) was two (8.0%) in ASPS, and SD was 80% (20/25), PD was 12% (3/25) and CR was 0% on site review. Adverse events of grade 3 or 4 occurred in 57.7% (15/26), and there was one patient who discontinued the treatment due to delay of administration by Herpes Zoster. The median number of nivolumab cycles was 10.5 (3-40), and the median PFS was 4.9 months (95% CI, 3.7-8.6 moths) and the median OS was 15.8 months (95% CI, 8.2-not reached) at data cut-off (1 year after the completion of registration, January 30, 2019).

Conclusion: The primary endpoint of response rate was not met for CCS and ASPS on central review. However, nivolumab showed good disease control rate of 64% (16/25) in patients with unresectable CCS and ASPS. Further studies are needed assessing the use of immune checkpoint inhibitors in this patient population, especially for ASPS.

Paper #02 3464044

EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN ALVEOLAR SOFT PART SARCOMA: RESULTS FROM A RETROSPECTIVE WORLD-WIDE REGISTRY

Nadia Hindi[1], *Evan Rosenbaum*[2], *Piotr Rutkowski*[3], *Hans Gelderblom*[4], *Kjetil Boye*[5], *Clemence Henon*[6], *Bruno Vincenzi*[7], *Andres Redondo*[8], *Javier Martinez-Trufero*[9], *Claudia Valverde*[10], *Jose Antonio Lopez-Martin*[11], *Paulina Jagodzinska*[3], *Elizabeth Connolly*[12], *William D. Tap*[2], *Javier Martin-Broto*[1]

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Objective: Alveolar soft-part sarcoma (ASPS) is an ultra-rare sarcoma subtype, with high metastatic potential, and frequently affects young adults. It is unresponsive to conventional cytotoxic drugs. Therapy with immune check-point (PD-1/PD-L1) inhibitors has shown modest benefit in unselected soft-tissue sarcoma, but responses in ASPS patients have been repeatedly reported in several clinical trials with PD-1/PD-L1 inhibitors. A world-wide registry has been established with the aim of exploring the efficacy of immune check-point inhibitors in ASPS.

Methods: We retrospectively collected data from adult patients diagnosed with ASPS and treated with PD-1/PD-L1 inhibitors for advanced disease in expert sarcoma centers from Europe, Australia and US. IRB approval has been obtained. Demographics, and data related to treatments and outcome were collected. Radiologic assessment was based on RECIST 1.1. Progression-free (PFS) and overall survival (OS) were calculated with Kaplan-Meier method. We present here a preliminary analysis of this series.

Results: 31 ASPS patients (17 female/14 male) with a median age of 30.8 years (range 20-59) were registered for this analysis. Primary tumor site was limbs in 25 (80%) and 22(71%) had metastasis at presentation. All patients received immune check-point inhibitors for metastatic disease. 24/31 (77%) had received previous systemic therapy (including 7 chemotherapy, 22 antiangiogenics), with a median of 2 previous lines (0-6). Immunotherapy regimens consisted of monotherapy in 18 patients and combination in 13 patients (9 with antiangiogenic agent). 12/31patients (38.7%) received immune check-point inhibitors within a clinical trial. From 21 preliminary evaluable patients, there was 1 complete response (CR) and 9 partial responses (PR) (ORR 47.6%). After a median follow-up of 15.8 months (1.6-33), 16/31 patients have progressed on immunotherapy, and the median PFS was 10.9 months (95% CI 9.9-11.9). Six patients have died. The median OS from start of immunotherapy was not reached and the 12-month and 24-month OS rates were 96% and 87% respectively. Patients achieving an objective response (CR+PR) had a significantly longer PFS when compared to those who achieved stable disease (not reached vs 10.3 months (95% CI 3.5-17.2), p= 0.047). We did not find differences in PFS between immunotherapy monotherapy and combination. Among 5 patients receiving immunotherapy at first line only one has progressed, whereas 15/26 patients who received immunotherapy in further lines have progressed, with a median PFS of 10.6 months (95% CI 8-13). Noteworthy, in those patients previously receiving antiangiogenics, the median PFS for pazopanib was 6.1 months (95%CI 3.6-8.6) and for sunitinib was 7.7 months (95% CI 2.2-13.2).

Conclusion: Therapy with immune check-point inhibitors was found to be active in metastatic ASPS. Our results would suggest that immune check-point inhibitors provide a longer disease control than antiangiogenics. This study is actively registering data in order to increase the knowledge of this highly promising family of drugs in ASPS.

Paper #03 3462142

FINAL ANALYSIS OF THE PHASE 1 TRIAL OF NY-ESO-1-SPECIFIC T-CELL RECEPTOR (TCR) T-CELL THERAPY (LETETRESGENE AUTOLEUCEL; GSK3377794) IN PATIENTS (PTS) WITH ADVANCED SYNOVIAL SARCOMA (SS)

Sandra D'Angelo[1], *George Demetri*[2], *Brian A. Van Tine*[3], *Mihaela Druta*[4], *John Glod*[5], *Warren Chow*[6], *Naimish Pandya*[7], *Aisha Hasan*[7], *Victoria L. Chiou*[7], *Jenna Tress*[7], *Julie Edwards*[8], *Tim Young*[7], *Mary Woessner*[7], *Alexandra Gyurdieva*[7], *Stefan Zajic*[7], *Sophia Goodison*[7], *Dejka Araujo*[9]

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Objective: NY-ESO-1–specific T cells (letetresgene autoleucel, abbreviated to lete-cel; GSK3377794) are autologous CD4+ and CD8+ T cells transduced with a self-inactivating lentiviral vector to express an engineered NY-ESO-1–specific TCR with greater binding affinity. Lete-cel has optimized recognition of HLA-A*02–presented peptides derived from NY-ESO-1, a cancer/testis antigen expressed in 70–80% of SS, to improve antitumor activity. NCT01343043 was a Phase I, open-label trial of lete-cel in pts with SS; final efficacy, safety, and persistence data are reported across all cohorts.

Methods: Pts with unresectable, metastatic, or recurrent SS who were intolerant/non-responsive to standard chemotherapy enrolled in 4 cohorts based on NY-ESO-1 tumor expression (high/low), were lymphodepleted and received lete-cel infusion; lymphodepletion regimen differed between cohorts (**Table 1**). The primary endpoint was investigator-assessed overall response rate (ORR) per RECIST v1.1; secondary endpoints included duration of response (DoR) and progression-free survival (PFS) per RECIST v1.1, overall survival (OS), and safety. Persistence of transduced cells was measured by quantitative PCR of transgene vector copies in DNA extracted from peripheral blood mononuclear cells. The study was not designed or powered to compare cohorts.

Results: Overall, 50 pts were enrolled; 45 received lete-cel infusion (modified intent-to-treat population). Demographics were similar between cohorts; approximately half of the pts were male, median age was 32 y (range 11–73), and most had stage IV disease. Median time in study was 480, 278, 605, and 643 days in Cohorts 1, 2, 3, and 4, respectively. At study completion, ORR ranged from 20% to 50% between cohorts; with 1 complete (lasting 34 weeks) and 14 partial responses (**Table 1**). In Cohorts 1, 2, 3, and 4, respectively, median DoR was 31.0, 8.6, 32.1, and 16.4 weeks and median PFS was 15.4, 13.1, 8.6, and 22.4 weeks (**Table 1**). At study completion, patients could enter long-term follow-up under a separate protocol. As of January 27, 2020, 2, 1, and 3 pts in Cohorts 1, 3, and 4, respectively, remain in follow-up; median OS for Cohorts 1, 2, and 3 was 24.3, 9.9, and 19.9 months, respectively; Cohort 4 median OS was not mature and will be reported later. Grade ≥3 adverse events (AEs) in ≥40% of pts in all cohorts were leukopenia, neutropenia, anemia, thrombocytopenia, and lymphopenia; Grade ≥3 serious AEs (SAEs) were most frequently febrile neutropenia, dyspnea, and neutropenia across cohorts (**Table 2**). AEs of special interest (AESI) included cytokine release syndrome (CRS) in 44% of pts (n=20) across cohorts (maximum Grade 1 in 9 pts, Grade 2 in 7 pts, Grade 3 in 3 pts, Grade 4 in 1 pt; 5 pts had CRS SAEs [Grade ≥3 in 2 pts]); all CRS AEs/SAEs resolved. AESI Guillain-Barré syndrome occurred in 2 pts; both were Grade 3 SAEs that resolved with sequalae. AESI multi-lineage cytopenias occurred in 96% of pts (n=43), maximum Grade 5 in 1 pt and Grade 3/4 in all others. Median duration of first cytopenia was 9.0 days (range 2–91). Peak persistence of transduced cells was generally higher in responders versus non-responders (**Table 1**); time to peak persistence was similar between these groups (median 8 days). No pts tested positive for replication competent lentivirus.

Conclusion: In pts with advanced SS who have a profound need for effective treatment options, lete-cel had a manageable safety profile; responses were recorded among all cohorts, but pts with high NY-ESO-1 expression and the more intensive lymphodepletion regimen received the greatest benefit. Based on these results, the IGNYTE-ESO master protocol trial (NCT03967223) was initiated in SS using high NY-ESO-1 expression criteria and the lymphodepletion regimen from Cohort 1.

Funding: GSK (study 208466; NCT01343043).

Table 1. NY-ESO-1 expression and lymphodepletion regimen in Cohorts 1–4, efficacy, and peak persistence in responders and non-responders; mITT population

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
mITT patients who were lymphodepleted and received ≥1 dose of lete-cel	n=12	n=13	n=5	n=15
NY-ESO-1 expression*	High	Low	High	High
Lymphodepletion regimen	High†	High†	High‡	Low§
Efficacy, n (%)				
Overall response rate¶ (95% CI)	6 (50) (0.21–0.79)	4 (31) (0.09–0.61)	1 (20) (0.01–0.72)	4 (27) (0.08–0.55)
Best overall response‖				
Complete response	1 (8)	0	0	0
Partial response	5 (42)	4 (31)	1 (20)	4 (27)
Stable disease	5 (42)	7 (54)	3 (60)	10 (67)
Progressive disease	1 (8)	1 (8)	0	1 (7)
Not evaluable	0	1 (8)	1 (20)	0
Median DoR (range), weeks	31.0 (13–72)	8.6 (8–13)	32.1 (32–32)	16.4 (14–94)
Median PFS (95% CI), weeks	15.4 (7.7–38.0)	13.1 (7.9–13.9)	8.6 (0.7–36.1)	22.4 (11.3–26.6)
Median OS (95% CI), months**	24.3 (8.5–48.8)	9.9 (3.9–19.6)	19.9 (8.8–NA)	Not mature
Peak persistence, median (range), DNA copies/µg				
Responders	106,174 (76,185–192,445)	65,875 (13,365–197,546)	123,314 (123,314– 123,314)	40,137 (5677–131,176)
Non-responders	30,601 (11,265–119,883)	72,564 (22,627–145,791)	15,688 (9453–43,015)	19,650 (164–111,260)

*Assessed by immunohistochemistry: high = score of 2+ or 3+ in ≥50% of tumor cells; low = score ≥1+ in ≥1% cells but not exceeding 2+ or 3+ in ≥50% cells.
†Fludarabine IV 30 mg/m^2/day × 4 days and cyclophosphamide IV 1800 mg/m^2/day × 2 days.
‡Cyclophosphamide IV 1800 mg/m^2/day × 2 days.
§Fludarabine IV 30 mg/m^2/day × 3 days and cyclophosphamide IV 600 mg/m^2/day × 3 days.
¶The proportion of patients with a confirmed complete or partial response relative to total number of patients.
‖Recorded from the time of first T-cell infusion until disease progression.
**Data from long-term follow-up protocol; data cut-off January 27, 2020.

DoR, duration of response; mITT, modified intent-to-treat; OS, overall survival; PFS, progression-free survival

Table 2. Number of patients with Grade ≥3 AEs in the mITT population*

Preferred term, n (%)	**Cohort 1 n=12**	**Cohort 2 n=13**	**Cohort 3 n=5**	**Cohort 4 n=15**
Any Grade ≥3 AE	**12 (100)**	**13 (100)**	**5 (100)**	**14 (93)**
Grade ≥3 AE in ≥25% of pts in any cohort				
Leukopenia†	11 (92)	12 (92)	5 (100)	11 (73)
Neutropenia†	10 (83)	11 (85)	4 (80)	10 (67)
Anemia†	10 (83)	11 (85)	3 (60)	7 (47)
Thrombocytopenia†	8 (67)	11 (85)	4 (80)	7 (47)
Lymphopenia†	12 (100)	8 (62)	3 (60)	6 (40)
Hypophosphatemia	9 (75)	5 (39)	2 (40)	3 (20)
Febrile neutropenia	4 (33)	4 (31)	0	6 (40)
Dyspnea	1 (8)	3 (23)	3 (60)	0
Hyponatremia	3 (25)	3 (23)	1 (20)	0
Any Serious Grade ≥3 AE	5 (42)	5 (38)	3 (60)	4 (27)
Serious Grade ≥3 AE in ≥3 pts				
Febrile neutropenia	2 (17)	1 (8)	0	2 (13)
Dyspnea	1 (8)	1 (8)	1 (20)	0
Neutropenia†	1 (8)	2 (15)	0	0

*From start date of lymphodepletion through end of study.
†Synonymous preferred terms are combined (leukopenia and white blood cell decreased; neutropenia and neutrophil count decreased; anemia and red blood cell count decreased; thrombocytopenia and platelet count decreased; and lymphopenia and lymphocyte count decreased).

AE, adverse event; mITT, modified intent-to-treat; SAE, serious adverse event.

Paper #04 3463188

DURABLE RESPONSES IN PATIENTS WITH SYNOVIAL SARCOMA IN THE PHASE I TRIAL OF ADP-A2M4 (MAGE-A4)

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Objective: This trial (NCT03132922) evaluated safety, tolerability, and antitumor activity of ADP-A2M4, genetically engineered autologous specific peptide enhanced affinity receptor (SPEAR) T-cells directed towards a MAGE-A4 peptide in patients (pts) with multiple solid tumor malignancies. Herein, follow-up data from pts with advanced synovial sarcoma is presented (n=16). The main portion of this trial is closed for enrollment, a low-dose radiation sub-study remains open.

Methods: This Phase I dose-escalation, expansion trial evaluated HLA-A*02 positive (excluding *02:05) pts with advanced cancers expressing MAGE-A4. Autologous T-cells were isolated, transduced with a lentiviral vector containing the MAGE-A4^{c1032} TCR, and expanded. Prior to infusion, pts received lymphodepletion with cyclophosphamide and fludarabine. Cohorts 1, 2, 3, and Expansion were to receive transduced cell doses of up to: 0.12 × 10^9, 1.2 × 10^9, 6 × 10^9, and 10 x 10^9, respectively. Disease was assessed per RECIST v1.1 by CT/MRI at wks 6, 12, 18, and 24, and every 3 months for 2 years, then every 6 months or until disease progression.

Results: As of Apr 2020, 16 pts with advanced synovial sarcoma were treated in either Cohort 3 or Expansion with a median transduced cell dose of 8.86 x10^9 (range: 3.41 to 9.97 x10^9). Median age was 49.0 yrs (range: 31 to 76) and median H-score of MAGE-A4 expression was 248.5 (range: 60.4 to 300). All pts received prior chemotherapy (median 2.5 regimens, range 1 to 6). Most common (>30%) AEs ≥Grade 3 were lymphopenia, leukopenia, neutropenia, anemia, thrombocytopenia, hypophosphatemia, and febrile neutropenia. Cytokine release syndrome (any grade) was reported in 13 pts (81%); the majority was Grade 1 or 2 (11 pts). One pt with synovial sarcoma had a Grade 5 SAE, (76-yr-old female; aplastic anemia) leading to modification of the lymphodepletion regimen and eligibility criteria. The Overall Response Rate was 44% and the Best Overall Response was PR (7), SD (7), PD (1), and pending (1). Responses were durable (median duration approximately 28 wks (range: 12 to 54$^+$ wks [PR at 54 wks ongoing]). Median OS had not been reached. SPEAR T-cells were detectable in peripheral blood and tumor tissue, and responded to antigen in vitro. Increases in T-cell infiltration, MHCI, and PD-L1 expression were observed in post-infusion tumor biopsies of some responding pts. Higher MAGE-A4 levels were associated with greater tumor reduction.

Conclusion: ADP-A2M4 induced clinical responses in pts with synovial sarcoma and had an acceptable safety profile. Transduced T-cells persist in vivo and remain functional. Analyses to determine factors that may influence response remain ongoing. These data support the ongoing SPEARHEAD-1 trial (NCT04044768).

10:30 am - 11:30 am – Special Awards Session –

YOUNG INVESTIGATOR AWARD WINNERS

Young Investigator Award 3464426

INCIDENCE OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MPNST) DEVELOPMENT IN PATIENTS WITH NF1 RECEIVING AND NOT RECEIVING MEDICAL THERAPIES DIRECTED AT PLEXIFORM NEUROFIBROMAS (PN)

Brittany Glassberg[1], *Andrea Gross*[1], *Eva Dombi*[1], *Andrea Baldwin*[1], *Trish Whitcomb*[1], *Ana Best*[1], *Amanda Carbonell*[1], *Kara Heisey*[1], *Janet Therrien*[1], *Oxana Kapustina*[1], *Brigitte C. Widemann*[1], *Hari Sankaran*[1]
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Objective: The MEK inhibitor (MEKi) selumetinib recently received FDA approval for pediatric patients with NF1 and symptomatic PN. Observation of MPNST in three patients on or after the NCI trial of selumetinib for PN raised the question of a potential association between MEKi therapy and MPNST development. Our objectives were to determine the proportion of malignant peripheral nerve sheath tumors (MPNST) in neurofibromatosis type 1 (NF1) patients enrolled on clinical trials at the NCI Pediatric Oncology Branch (POB) by the type of PN-directed medical treatment received, and to adjust for risk factors associated with MPNST development.

Methods: We conducted a retrospective review of all patients with NF1 enrolled on natural history and treatment trials directed at NF1 plexiform neurofibromas (PN) at the NCI POB from 1/1/1998 to 1/1/2020, excluding patients referred for treatment of MPNST. Patients were categorized into 4 groups: 1) History of MEKi therapy, 2) treatment with medical therapy other than MEKi, 3) treatment with both MEKi and non-MEKi therapies, and 4) no PN directed medical therapy. Proportions of MPNST rates were calculated for each group, as well as sex and median age to MPNST development. For the patients with a history of PN-directed therapy, a time-dependent Cox regression model was used to generate hazard ratios and 95% CI to assess associations between risk factors and MPNST development including radiation exposure, surgical history (debulking and PN resection), age of treatment initiation, family history of MPNST, and diagnosis of sporadic vs familial NF1.

Results: 296 patients (54% male) with diagnosis of NF1 (median age of enrollment 13.6 years, range 0.2-61.0 years) were identified, of which 34 (11.5%) developed MPNST. MPNST rates were lower in the MEKi group (n=0/29, 0%) and both MEKi and non-MEKi group (n=3/45, 6.7%), compared to the non-MEKi therapy alone (n=12/91, 13.2%) and no PN-targeted treatment group (n=19/131, 14.5%), as seen in Figure 1. The median age of MPNST development was earlier in the both MEKi and non-MEKi group (12.7 years) compared to the non-MEKi alone and no treatment groups (16.6 years and 24.9 years, respectively). On univariate analysis, only radiation exposure (HR, 11.8[95% CI: 3.6-38.4]; $p < 0.01$), was significant whereas family history of MPNST (HR, 5.82[95% CI: 0.7-49.5], p=0.9), history of familial NF1 (HR, 2.2[95% CI: 0.7-7.3]; p=0.2), PN resection history (HR, 2.1 [95% CI:0.7-7.0]; p=0.2), MEK vs non-MEKi treatment group (HR, 0.94[95% CI:0.26-3.41]; p=0.9), age of treatment initiation (HR, 1.0[95% CI:0.92-1.09]; p=1.0), debulking surgical history (HR, 1.02 [95% CI: 0.35-2.95]; p=1.0) were not significant risk factors for MPNST development.

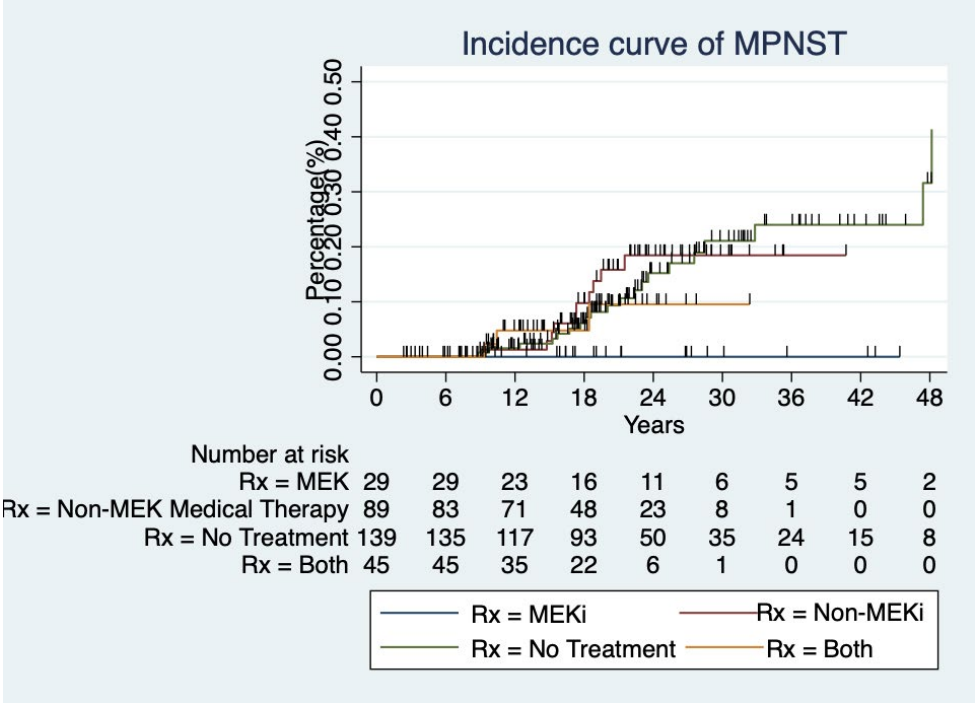
Conclusion: In this high-risk study population of patients with NF1 PN, more events of MPNST were seen in patients who had not received PN-directed medical therapy or had received non-MEKi PN-directed therapy compared to those with a history of MEKi therapy. Patients treated with MEKi therapy developed MPNST at a younger age than those in other groups. Radiation exposure is an important risk factor that may contribute to the development of MPNST in patients with a history of PN-directed medical therapy. This study is limited by the relatively small sample size and the short follow-up time of patients with a history of MEKi therapy (compared to those with a history of non-MEKi therapy) given its recent approval for use in NF1 patients with PN, making inference into the earlier age of onset of MPNST in this group difficult. However, our analysis was able to demonstrate no large difference in risk of MPNST between treatment groups. In the future, significant variables on univariate analysis will be examined in a multivariate model, and the final statistical model will be validated using data from a more generalizable NF1 cohort. Patients on MEKi therapy will be followed to assess for changes in MPNST development and associated risk factors after a longer duration of treatment.

Incidence of MPNST by Treatment Group

MPNST History	Treatment Group				
	MEKi Therapy (# of patients)	Non-MEKi Therapy (# of patients)	Both MEKi and non-MEKi (# of patients)	No Treatment (# of patients)	Total (# of patients)
No (# of patients)	29	79	42	112	262
Yes (# of patients)	0	12	3	19	34
Total (# of patients)	29	91	45	131	296
% of patients with MPNST	0.00%	13.19%	6.67%	14.50%	11.49%

Incidence of MPNST development separated by treatment group.

Incidence of MPNST development separated by treatment group. Blue line represents patients with history of MEKi PN-directed therapy alone, orange line represents patients with history of both MEKi and non-MEKi PN-directed therapies, green line represents patients with history no PN-directed medial therapy, and red line represents patients with history of non-MEKi PN-directed therapy. Number of patients per group and incidence percentages are found in Table 1.



10:30 am - 11:30 am – Special Awards Session –

YOUNG INVESTIGATOR AWARD WINNERS

Young Investigator Award 3465542

THE ASPSCR1-TFE3 TRANSCRIPTIONAL COMPLEX IN ALVEOLAR SOFT PART SARCOMAGENESIS

Shiv Verma[1]*; Amir Pozner*[1]*; Li Li*[1]*; Shuxin Wang*[2]*; Jared J. Barrott*[1]*; Sarmishta Kannan*[1]*; Jamie Yu*[3]*; Sydney L. Lambert*[1]*; Alexander Lazar*[4]*; Martin Hirst*[5]*; Torsten O. Nielsen*[3]*; Peter S. Shen*[2]*; Kevin B. Jones*[1]
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Objective: Transcription in alveolar soft part sarcoma (ASPS) is orchestrated by the fusion oncoprotein, ASPSCR1-TFE3 (AT3), the product of a gene fusion created by a t(X;17) chromosomal translocation. Shared transcriptomic features across species underscore the role of AT3 as a reprogramming or pioneer factor. AT3 transcriptional reprogramming biology therefore begs additional interrogation. How the ASPSCR1 amino terminus prompts transcriptional activation at AT3 target loci in the absence of the TFE3 activation domain has remained unknown.

Methods: Proteomics of co-immunoprecipitating AT3 was performed in human cell lines and mouse tumors and candidate interactions tested by further IP and Westerns and proximity ligation assays. Chromatin immunoprecipitation (ChIP) for AT3 and a putative co-factor tested co-localization on chromatin. Functional assays following knock-down or overexpression of AT3 and/or the putative co-factor tested the impact on transcriptome and genome organization by HiChIP. In addition, electron microscopy was used to define the three-dimensional complex shape. Co-expression of another protein capable of disassembling the complex was also tested for transcriptional impact.

Results: Proteomics of co-immunoprecipitating ASPSCR1-TFE3 revealed a strong enrichment of VCP/p97, an AAA+ ATPase with known segregase function. VCP also co-distributed across the genome-breadth of chromatin with ASPSCR1-TFE3 and there associated with active enhancers, indicated by flanking peaks of H3K27ac that assemble into higher order chromatin structures by HiChIP. Positive and negative genetic experiments with ASPSCR1-TFE3 and VCP demonstrated that they function co-dependently for cancer cell proliferation, colony formation, enhancer activation, chromatin conformation, and transcription. The VCP associating with ASPSCR1-TFE3 was found by native gel and electron microscopy to be assembled into homo-hexamers. Specific disruption of VCP hexamer assembly inhibited the transcriptional impact of ASPSCR1-TFE3.

Conclusion: VCP/p97, a segregase enzyme was found to gather in chromatin, driving 3-dimensional structures as a co-factor of transcriptional regulation in alveolar soft part sarcoma.

11:30 am - 12:30 am – Session 3 –

LEIOMYOSARCOMA AND UNDIFFERENTIATED PLEOMORPHIC SARCOMA

Paper #05 3465673

UPDATED PHASE I STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RIVOCERANIB (APATINIB) AND NIVOLUMAB IN PATIENTS WITH UNRESECTABLE OR METASTATIC CANCER

Sant P. Chawla[1], *Victoria Chua-Alcala*[1], *Steven M. Wong*[1], *Doris Quon*[1], *Ania M. Moradkhani*[1], *Kelly Wang*[1], *Ish Bhuiyan*[1], *Olivia Pelenghian*[1], *Sandon Scott*[1], *Natalie Krkyan*[1], *Kitty Zheng*[1], *Steven Norton*[2], *Kehua Wu*[2], *Ted M. Kim*[1], *Erlinda M. Gordon*[1]
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Objective: Anti-angiogenic drugs have been clinically investigated in combination with anti-PD-1 therapies due to their synergistical immune-modulatory effects. We conducted a 2-part phase I clinical trial in order to evaluate the safety, tolerability and efficacy for the combined treatment with nivolumab (an FDA approved CPI) and rivoceranib (also known as apatinib), a highly-selective VEGFR-2 tyrosine kinase inhibitor, in patients with locally advanced unresectable/metastatic solid tumors. We have previously reported preliminary results. With emerging data, we herein present safety and efficacy results for entire study.

Methods: The design included a 3+3 dose escalation trial (part I) followed by an expansion cohort (part II). In part I, escalating doses of rivoceranib starting from 400 po qd were applied in combination with nivolumab at 240 mg iv q2w. Meanwhile, two additional cohorts received rivoceranib at 300 and 200 mg (concomitant with nivolumab) respectively. All the patients in part II initially received 300 mg rivoceranib in combination with nivolumab therapy at 240 mg q2w. While, some received reduced dose of nivolumab (200 mg) in later treatments. Main eligibility criteria include patients with primary diagnosis of histologic- or cytologic-confirmed solid tumor cancer.

Results: A total of 30 patients were recruited where 10 patients participated in part I and 20 patients in part II. Tumor types are listed in Table 1. Grade 3 and greater treatment-related treatment-emergent Adverse Events (TEAEs) occurred in 23 (76.7%) patients (7 patients from Part 1 and 16 patients from Part 2). Fatigue (10.0%), hypertension (10.0%), nausea (10.0%), anaemia (16.7%) and asthenia (10.0%) were the grade ≥ 3 TEAEs occurring in ≥10% of patients. Two patients (6.7%) experienced fatal AEs. There were no unexpected side effects, no additive side effects of the combined treatment (nivolumab and rivoceranib), and no drug related death noted. Reasons of discontinuation were toxicity in 9 patients (30.0%; 4 from Part 1 and 5 from Part 2) and dose reduction was applied in 9 patients due to AEs (30.0%%; 3 from Part 1 and 6 from Part 2). Three patients experienced 4 dose-limiting toxicities, including grade 3 non-hematology toxicity (DL4 and DL5) and uncontrollable hypertension defined as stage 2 hypertension (DL4). The overall response rate (ORR) was 13.3% (95% CI: 3.8 % to 30.7 %), and the disease control rate (complete response+ partial response+ stable disease) was 76.7% (95% CI: 57.7 % to 90.1 %). The median progression-free survival (PFS) was 7.2 months (95% CI: 5.3 to 9.0 months). Partial response was observed in 4 patients (13.3%). Clinical trial information: NCT03396211.

Conclusion: The results indicate the potential clinical benefit of rivoceranib combination with nivolumab in unresectable/metastatic solid tumors with a tolerable safety profile.

Table 1. Tumor Type

	Part I	Part I	Part I	Part II (n=20)	Total (n=30)
	400mg (n=3)	300mg (n=7)	Combined 400mg and 300mg (n=10)		
Angiosarcoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (15.0%)	3 (10.0%)
Cervical cancer (squamous cell carcinoma)	0 (0.0%)	1 (14.3%)	1 (10.0%)	1 (5.0%)	2 (6.7%)
Cholangiocarcinoma	0 (0.0%)	1 (14.3%)	1 (10.0%)	0 (0.0%)	1 (3.3%)
Chondrosarcoma	0 (0.0%)	1 (14.3%)	1 (10.0%)	2 (10.0%)	3 (10.0%)
Fibrous histiocytoma	1 (33.3%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (3.3%)
Gastric cancer	0 (0.0%)	1 (14.3%)	1 (10.0%)	2 (10.0%)	3 (10.0%)
Leiomyosarcoma	1 (33.3%)	1 (14.3%)	2 (20.0%)	7 (35.0%)	9 (30.0%)
Liposarcoma	0 (0.0%)	1 (14.3%)	1 (10.0%)	0 (0.0%)	1 (3.3%)
Malignant spindled and epithelioid sarcoma	0 (0.0%)	1 (14.3%)	1 (10.0%)	0 (0.0%)	1 (3.3%)
Osteosarcoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (10.0%)	2 (6.7%)
Synovial sarcoma	1 (33.3%)	0 (0.0%)	1 (10.0%)	3 (15.0%)	4 (13.3%)

Paper #06 3463196

LINEAGE-DEFINED LEIOMYOSARCOMA SUBTYPES EMERGE YEARS BEFORE DIAGNOSIS, DETERMINING PATIENT SURVIVAL

Nathaniel Anderson[1], *Yael Babichev*[2], *Fabio Fuligni*[1], *Federico Comitani*[1], *Mehdi Layeghifard*[1], *Rosemarie Venier*[2], *Anant Maheshwari*[1], *Sheena Guram*[2], *Claire Wunker*[2], *J. Drew Thompson*[1], *Marcus Bernadini*[3], *Jay Wunder*[2], *Irene Andrulis*[2], *Peter Ferguson*[4], *Albiruni Abdul Razak*[3], *Carol J. Swallow*[2], *Rima Al-Awar*[5], *Richard Marcellus*[5], *Marjan Rouzbahman*[3], *Daniel Durocher*[2], *Ludmil Alexandrov*[6], *Brendan Dickson*[2], *Rebecca Gladdy*[2], *Adam Shlien*[1]
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Objective: Leiomyosarcoma (LMS) is a malignant neoplasm of smooth muscle differentiation. The heterogeneity of its site of origin and clinical course, including the development of metastasis and response to therapy, makes the treatment of LMS particularly challenging. Currently, LMS treatment is not informed by molecular subtyping and is associated with highly variable survival. While disease site represents an important prognostic factor, the contribution of genetic factors to LMS subtype, origins or timing are mostly unknown. For these reasons, the objective of this study is to investigate the mutational processes underlying primary and metastatic LMS.

Methods: We carried out an analysis of the patterns, location and evolution of somatic mutations in LMS - both between and within tumors. In total, we analyzed 70 whole-genomes and 130 transcriptomes of LMS to detect somatic mutations, including substitutions, small insertions or deletions, copy number changes, structural rearrangements as well as clustered and complex events.

Results: Although labeled as a single disease characterized by smooth muscle differentiation, the clinical presentation and behavior of LMS is inconsistent. To determine to what degree this variability is explained by overall genomic and transcriptomic features, we began by examining the tumors' whole transcriptomes and found three predominant gene expression subtypes which were found to originate from distinct lineages of smooth muscle cells. Of these, dedifferentiated LMS with high immune infiltration and LMS of gynaecological origin acquired the highest burden of genomic mutation at the fastest rate, and are associated with worse survival. Subsequent whole-genome profiling highlighted the extremely early origins of LMS and widespread genetic diversity within primary tumors and between metastatic relapses, especially with respect to rearrangements and clustered mutations. Homologous recombination defects lead to genome-wide mutational signatures, and a corresponding sensitivity to PARP and other DNA damage response inhibitors, suggesting a novel therapeutic strategy for LMS. Finally, by phylogenetic reconstruction, we present evidence that clones seeding lethal metastases arise decades prior to LMS diagnosis.

Conclusion: Our findings provide insights into the pathogenesis and natural history of LMS. The results presented in this study provide compelling support for molecular subtyping in this cancer type, evidence for extremely early systemic spread in LMS, and highlights the potential use of a DNA damage inhibitors as a promising therapeutic avenue for these patients.

Paper #07 3464097

IS SITE OF ORIGIN (IVC VS. NON-IVC) PROGNOSTIC FOLLOWING RESECTION OF PRIMARY RETROPERITONEAL LEIOMYOSARCOMA (RP LMS)? COMBINED EXPERIENCE OF TWO SARCOMA REFERRAL CENTRES

Nicolas A. Devaud[1], *Deanna Ng*[1], *Harini Suraweera*[1], *Abha A. Gupta*[2], *Albiruni Razak*[2], *Peter Chung*[3], *Savtaj Brar*[1], *Thomas Lindsay*[1], *Rebecca Gladdy*[1], *Ian McGilvray*[1], *Claudia Sangalli*[5], *Roberta Sanfilippo*[4], *Silvia Stacchiotti*[4], *Dario Callegaro*[6], *Marco Fiore*[6], *Alessandro Gronchi*[6], *Carol J. Swallow*[1]
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Objective: The majority of LMS that originate in the retroperitoneum (RP) are thought to arise from smooth muscle-walled veins, including large named veins and smaller tributaries. In addition to posing unique technical challenges to complete resection, LMS of the Inferior Vena Cava (IVC) could hypothetically have a different biology to non-IVC LMS. Here we compare the treatment and outcomes of IVC vs. non-IVC LMS of the RP managed at two major sarcoma referral centres over a 20-year interval.

Methods: Consecutive patients with primary RP LMS who underwent resection between 01/97 and 12/18 were identified from prospective databases, and charts retrospectively reviewed to ascertain additional patient-, tumour-, treatment- and outcome- related details. Overall and disease-specific survival (OS, DSS) curves were constructed by the Kaplan-Meier method. Crude cumulative incidence (CCI) of local and distant recurrence (LR, DR) were calculated within a competing risk framework.

Results: A total of 187 patients who underwent resection of primary RP LMS were identified; 8 who had synchronous distant metastases were excluded from further analysis, leaving a study cohort of 179 patients (centre A, n=67; centre B, n=112). There were two notable differences between the centres: preoperative radiotherapy was given to 71% and 19% of patients at centres A and B, respectively, and the proportion of patients scored as having FNCLCC grade 3 LMS was twice as high at centre B. There were no differences in R2 rate, follow-up time, OS, DSS, LR or DR between the centres. For the study cohort of 179 patients, median age at time of resection was 58, 67% were female, and median follow-up time was 45 months. Site of origin was IVC in 76 and non-IVC in 103 patients (Table). Patient characteristics and tumour grade were similar between IVC and non-IVC groups, while tumour size was greater in the non-IVC group (p=0.0045). IVC and non-IVC RP LMS were managed similarly, except for more complex vascular reconstructions after caval resection, including cold hepatic perfusion in 5 patients and cardiopulmonary bypass in one other.

There was no significant difference in 90-day mortality between the IVC and non-IVC groups.

OS and DSS at 5 years following resection were 65% and 68%, respectively, and did not differ significantly between IVC and non-IVC groups, though there was a trend in favour of IVC tumours (Fig. 1). DR was common, LR was uncommon, and both occurred at similar rates in the two groups (Fig. 2). OS following the development of DR was higher in the IVC than non-IVC group (67% vs. 35% at 3 years, p= 0.02, Fig. 3).

Conclusion: This large experience with RP LMS at two reference centres has revealed a potential difference in biologic aggressiveness depending on site of origin, interestingly in favour of the IVC site. This could be related to derivation from vascular smooth muscle, a hypothesis that will be examined further. Aggressive management of RP LMS is associated with excellent local control.

Comparison of IVC and Non-IVC derived Retroperitoneal Leiomyosarcoma

	all N=179	IVC N=76	Non-IVC N=103	p-value
Age, years median (range)	58 (27-82)	60 (28-82)	58 (27-81)	0.937
Gender Male Female	33% (59/179) 67% (120/179)	36% (27/76) 64% (49/76)	31% (32/103) 69% (71/103)	0.641
Tumour Size, max diameter, cm median (range)	11(3-32)	10(3-30)	12(3-32)	0.0045
FNCLCC grade - I - II - III - Not reported	8% (14/179) 38% (69/179) 48% (86/179) 6% (10/179)	8% (6/76) 34% (26/76) 50% (38/76) 8% (6/76)	8% (8/103) 42% (43/103) 46% (48/103) 4% (4/103)	0.711
Number organs resected, median (range)	2(0-9)	2(0-6)	3(0-9)	0.592
Treatment: - Tri modality (NeoCTx + NeoRadTx +Resection) (NeoCTx + Resection + AdjRadTx) - RadTx + Resection: NeoRadTx + Resection Resection + AdjRadTx - CTx + Resection: NeoCTx + Resection Resection + AdjCTx - Resection only	19% (34/179) 32/179 2/179 21% (37/179) 33/179 4/179 26% (47/179) 28/179 19/179 34% (61/179)	25% (19/76) 19/76 0/76 21% (16/76) 15/76 1/76 24% (18/76) 13/76 5/76 30% (23/76)	15% (15/103) 13/103 2/103 20% (21/103) 18/103 3/103 28% (29/103) 15/103 14/103 37% (38/103)	
Resection status - R0/R1 - R2	98% (176/179) 2% (3/179)	97% (74/76) 3% (2/76)	99% (102/103) 1% (1/103)	0.847
Follow-Up Time, months median (range)	45 (1-258)	47 (1-220)	42 (1-258)	0.644
90-d Mortality	1.7% (3/179)	1.3% (1/76)	1.9% (2/103)	0.243
5-yr Disease Specific Survival	68% (60-76)	74% (64-87)	63% (53-75)	0.1
5-yr Overall Survival	65% (57-73)	70% (60-83)	62% (51-73)	0.2
5-yr CCI Local Recurrence	5% (2-9)	6% (1-11)	5% (1-9)	0.611
5-yr CCI Distant Recurrence	56% (48-64)	53% (40-65)	58% (48-69)	0.515

Fig 1A. Overall Survival of RP LMS by site of Origin (IVC vs Non-IVC)

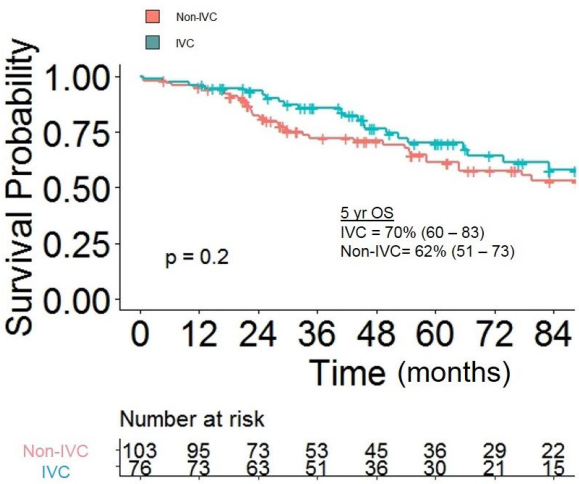


Fig 1B. Disease-Specific Survival of RP LMS by site of Origin (IVC vs Non-IVC)

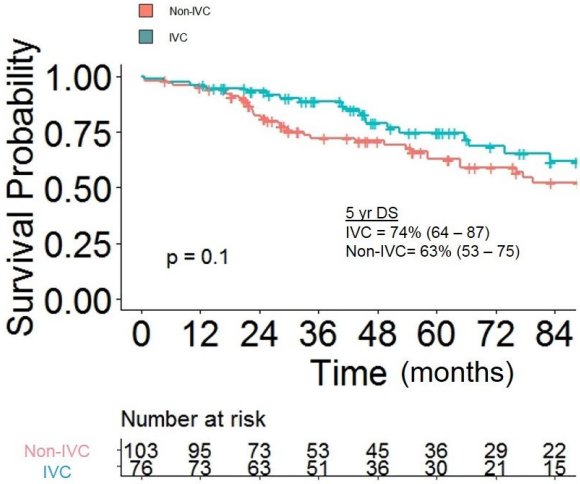


Fig 2A. Local Recurrence of RP LMS by site of Origin (IVC vs Non-IVC)

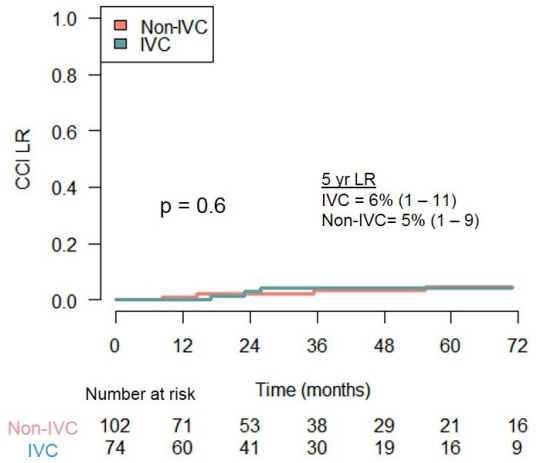


Fig 2B. Distant Recurrence of RP LMS by site of Origin (IVC vs Non-IVC)

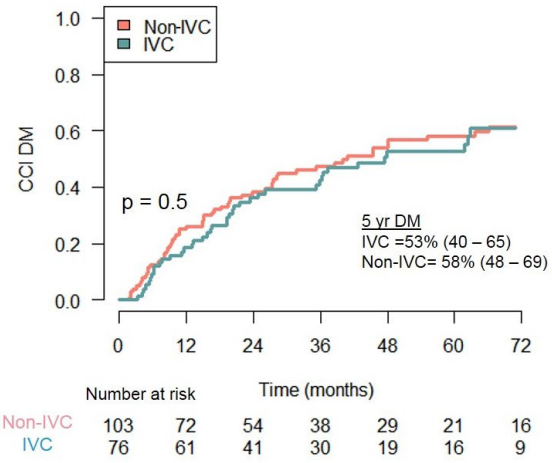
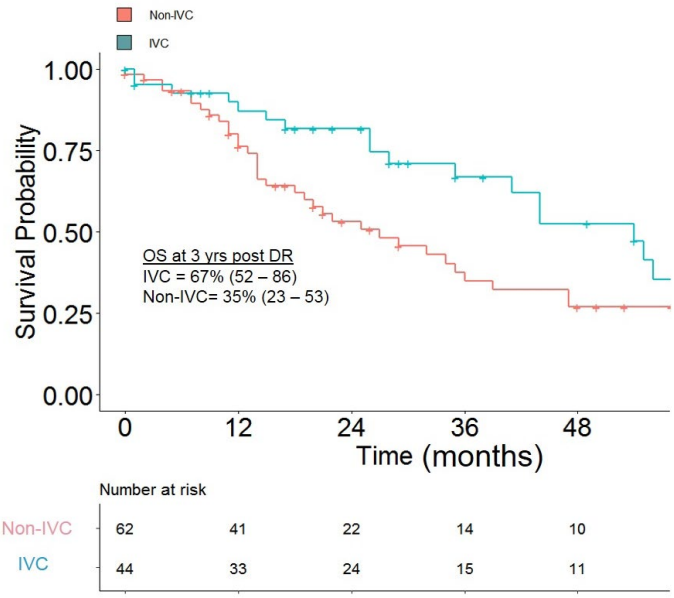


Fig 3. Overall Survival following Distant Recurrence by site of Origin (IVC vs Non-IVC)



Paper #08 3457194

HOMOLOGOUS RECOMBINATION DNA REPAIR AND LOSS OF HETEROZYGOSITY IN LEIOMYOSARCOMA

Nathan D. Seligson[1], *Sherri Z. Millis*[3], *Dexter Jin*[3], *Nicholas Grosenbacher*[2], *Monica P. Bennett*[1], *Alexander M. Litvintchouk*[1], *Colin M. Stets*[2], *Julia A. Elvin*[3], *John L. Hays*[2], *James Chen*[2]
[1]*University of Florida, Jacksonville, Florida, UNITED STATES;* [2]*Ohio State University, Columbus, Ohio, UNITED STATES;* [3]*Foundation Medicine Inc, Cambridge, Massachusetts, UNITED STATES*

Objective: Leiomyosarcoma (LMS) is a rare, aggressive subtype of soft-tissue sarcomas (STS) with limited treatment options available to patients. Targeted therapies exist to leverage homologous recombination (HR) pathway deficiencies in tumors (HRD) compared to HR proficient tumors (HRP); however, their prevalence and role have not been fully described in STS. Previous studies have identified enriched populations within LMS, including uterine LMS. Here we present the largest assessment of alterations in HR genes and their clinical consequences.

Methods: Comprehensive genomic profiling of 1,672 LMS were obtained through Foundation Medicine's research database. Samples were sequenced by hybrid capture-based comprehensive genomic profiling. Genome-wide loss of heterozygosity (LOH) was evaluated as a marker of HRD. An HRD phenotype was defined by a LOH score of >14% (LOH-High). Genes associated with the HR pathway were identified from previously published studies. Clinical data for 70 patients with LMS treated at the Ohio State University Comprehensive Cancer Center were included to assess clinical correlates with genomic findings. Descriptive statistics, chi-squared test, and Kruskal-Wallis test were used as appropriate. All data were analyzed in Rv3.5.1. p values <0.05 were considered statistically significant.

Results: In the full set of 1,672 LMS, the mean LOH was 12.8±7.0% with 658 (39.4%) samples exhibiting an LOH-High score. Uterine LMS exhibited an increased prevalence of the LOH-High samples compared to non-uterine LMS (uterine LMS: 288, 44.3%; non-uterine LMS: 370, 36.2%; p=0.0002). *BRCA1/2* biallelic loss was associated with an elevated LOH compared to any other molecular categorization of LMS (*BRCA1/2* biallelic loss: 18.8±7.3%, non-*BRCA1/2* HR biallelic loss: 13.4±7.1%; All HR monoallelic loss: 11.1±5.0%; HR wildtype: 12.7±6.9%; p<0.001; **Figure 1**). *BRCA1/2* biallelic loss was highly associated with the LOH-High phenotype (p=0.001) and was identified in 4.38% of LOH-High compared to 1.02% of LOH-Low samples. The LOH-High phenotype was also associated with tumors harboring *RB1* genomic variants (p<0.03); however, *TP53* variants were not associated the LOH-High phenotype (p=0.5).

Conclusion: LMS is a heterogeneous disease with multiple known molecular subtypes. Deficiencies in the HR pathway genes have been identified as enriched within LMS. These data suggest that a significant portion of LMS patients may have phenotypic or genomic identifiers of HR pathway deficiencies. Further analysis, including survival analysis, is underway.

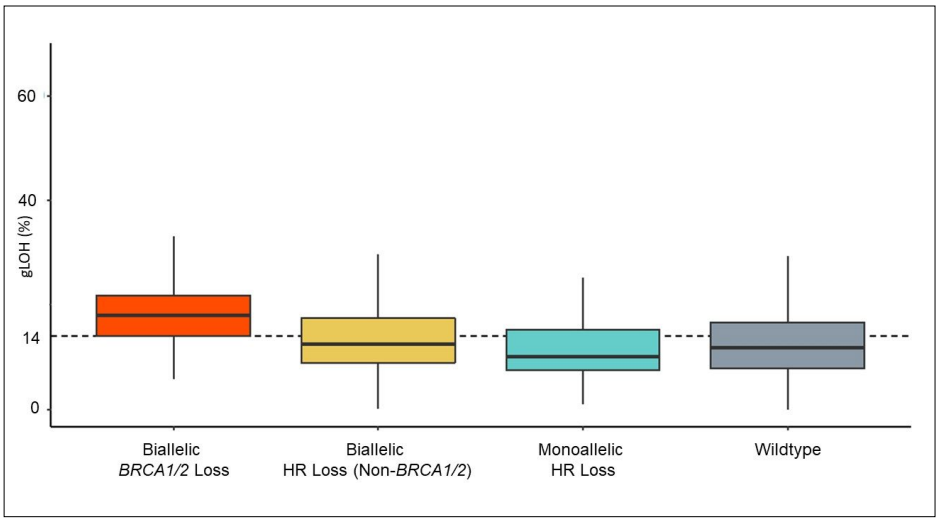


FIGURE 1: Biallelic loss of *BRCA1/2* correlated to higher gLOH compared to biallelic loss of non-*BRCA1/2* HR genes, monoallelic loss of any HR gene, or wildtype HR (*BRCA1/2* biallelic loss: 18.8±7.3%, non-*BRCA1/2* HR biallelic loss: 13.4±7.1%; All HR monoallelic loss: 11.1±5.0%; HRR wildtype: 12.7±6.9%; p<0.001).

12:30 pm - 1:30 pm – Session 4 –

OSTEOSARCOMA AND PEDIATRIC BONE SARCOMAS

Paper #09 3437417

A COMPARISON OF ONCOLOGICAL AND SURGICAL OUTCOMES IN ENDOPROSTHETIC RECONSTRUCTION VERSUS ROTATIONPLASTY FOR PAEDIATRIC LOWER EXTREMITY BONE SARCOMA

Jong Min Lee[2], *Jonathan R. Perera*[1], *Eliane R. Trottier*[2], *Sevan Hopyan*[2], *Kim Tsoi*[1]
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[2]*Paediatric Orthopaedics, SickKids, Toronto, Ontario, CANADA*

Objective: Paediatric bone sarcomas around the knee requiring articular surface resections are often amenable to either endoprosthetic reconstruction or rotationplasty. Cosmetic normality and durability dramatically distinguish these two options, although patient-reported functional satisfaction has been similar among survivors. However, the impact on oncological and surgical outcomes for these approaches has not been directly compared.

Methods: We retrospectively reviewed all wide resections from primary bone sarcomas of the distal femur or proximal tibia that were reconstructed either with an endoprosthesis or by rotationplasty at our institution between Jan 2004 and Dec 2017 with a minimum 2-year follow-up. Demographic information and clinical data were compared using Chi-squared tests for categorical data and unpaired t-test for numerical data. Survival analysis was performed on patients without metastases using the Kaplan-Meier method with statistical significance set at $p<0.05$.

Results: Fifty patients with primary bone sarcomas around the knee underwent wide resection and either endoprosthetic reconstruction (n=26) or rotationplasty (n=24). Groups were comparable in terms of demographic parameters, systemic tumour burden including metastatic disease and tumour volume at presentation. Every patient received neoadjuvant chemotherapy as per institution protocol with similar necrotic responses histologically in both groups. We found that selection of endoprosthetic reconstruction versus rotationplasty did not impact the five-year overall survival amongst patients who presented without metastasis and the choice of the surgery was heavily patient led.

Local recurrence was greater in endoprosthesis group, with 3 recurrences compared to 0 in rotationplasty group (p=0.09). The five-year overall survival was 51.4% and 67.9% in the endoprosthesis and rotationplasty groups, respectively (p=0.864). When only patients with greater than 90% chemotherapy-induced necrosis were considered the overall survival was better in the rotationplasty group. Even with these low numbers the difference in local recurrence doesn't account for the overall survival difference which was significantly better in the rotationplasty group when compared with the endoprosthesis group, 100% vs. 37.5% at five years, p=0.03, shown in figure 2.

When surgical outcomes were considered, a higher complication rate was seen in patients that received an endoprosthesis compared to those who underwent rotationplasty. Looking at the reoperation rate, 42.3% (n=11) of the endoprosthesis patients required a minimum of one additional surgery compared with only 29.2 % (n=7) among rotationplasty patients (p=0.33). The most common reasons for re-operation in endoprosthesis patients were wound breakdown (n=8), periprosthetic fracture (n=2), and vascular complications (n=2). Excluding limb length equalisation procedures, the average time to re-operation in this patient population was 5.6 months (range 1 week to 23 months). The most common reason for a secondary procedure in rotationplasty patients were secondary to vascular complications (n=2) and hardware irritation (n=2), with the vascular compromise being more immediate and hardware a more chronic issue.

Conclusion: Our cohort is the largest in the literature to date and confirms that endoprosthetic reconstruction and rotationplasty are both viable limb-salvage options for reconstruction after resection of bony sarcomas around the knee in the paediatric population.

While an endoprosthesis may provide a more traditional result, it is associated with a higher complication rate and of additional surgical intervention. Endoprosthesis reconstruction may also negatively impact local recurrence. This shows that

in these patients where limb salvage is extremely challenging, using rotationplasty as an alternative to reconstruction is a viable option. We will need to complete the assessment using functional and psychological assessment scores to assess the differences further.

Figure 2 – 5 year overall Survival in patients who presented without metastasis

	Endoprosthesis n = 9	Rotationplasty n = 7
5 year overall survival (%) p = 0.0289	37.5	100

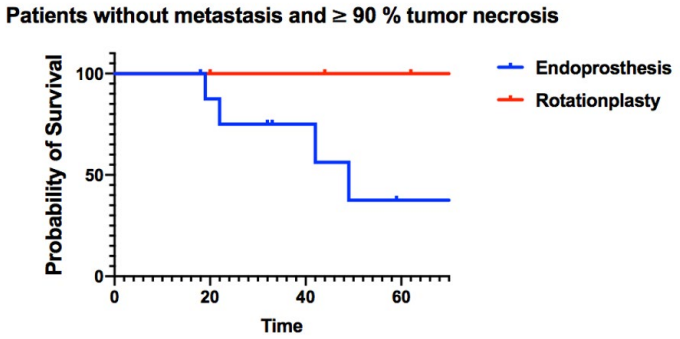


Figure 2 – 5 year overall Survival in patients who presented without metastasis

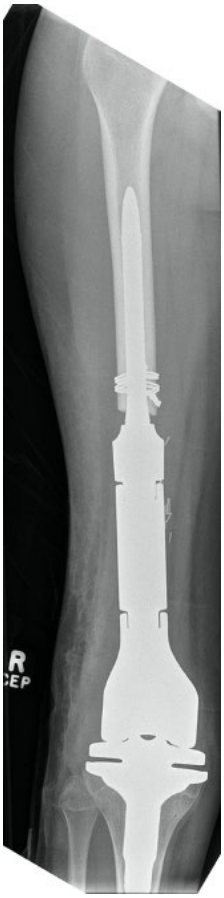
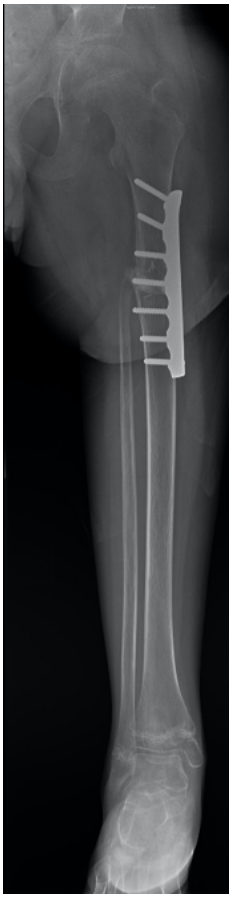


Figure 1 – Xray examples of rotationplasty vs endoprosthesis

Figure 1 – Xray examples of rotationplasty vs endoprosthesis



Paper #10 3464085

EXPRESSION PROFILING AND SPATIAL LOCALIZATION OF CD45+ LEUKOCYTES INFILTRATING PRIMARY AND RELAPSED BONE SARCOMAS

Anthony Cillo[2], Elina Mukherjee[3], Sayali Onkar[2], Kurt R. Weiss[4], Melissa A. Burgess[5], Tanya Heim[4], Dario Vignali[2], Tullia Bruno[2], ***Kelly Bailey***[1]

[1]Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, UNITED STATES; [2]Immunology, Univeristy of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, UNITED STATES; [3]Pediatrics, University of Pittsburgh, Pittsburgh, Pennsylvania, UNITED STATES; [4]Orthopaedic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, UNITED STATES; [5]Medicine, University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, Pennsylvania, UNITED STATES

Objective: Patients with relapsed bone sarcomas continue to have very poor overall survival. Very little is currently understood about the bone sarcoma immune microenvironment and changes in immune cell infiltration, organization and function at the time of relapse. The goals of this work were to determine: 1) the feasibility of performing single-cell (sc) RNAseq on fresh bone sarcoma biopsy tissue and patient paired peripheral blood 2) the expression profiles of immune cells infiltrating primary and relapsed bone sarcomas and 3) the spatial organization of leukocytes within bone sarcomas using multiplexed immunohistochemistry. We hypothesized that relapsed bone sarcomas would demonstrate enhanced immune cell infiltration and activation given prior exposure to DNA damage (chemotherapy, radiation).

Methods: Bone sarcoma patients consented for enrollment in the IRB-approved Musculoskeletal Tumor Oncology Registry and Tissue Bank (MOTOR) at The University of Pittsburgh had tumor cores and peripheral blood collected at the time of planned diagnostic biopsy. scRNAseq was performed on flow sorted CD45+ live cells from fresh tumor biopsy material and paired patient peripheral blood using an IRB-approved protocol. Samples from relapsed tumors were all minimally 6 months from last chemotherapy administration. A cohort of "normal" adolescent peripheral blood from anonymous blood bank donors (ages 16-18) was also subjected to scRNAseq analysis to generate a reference adolescent peripheral blood mononuclear cell (PBMC) dataset. Briefly, tumors were digested into single cell suspensions, labeled and flow sorted to capture the CD45+ cell population within the tumor biopsy. A minimum of 7,000 live, CD45+ cells per condition were prepared for scRNAseq analysis using a 10x Genomics platform. Sequencing was performed using a NextSeq500. Samples were demultiplexed and processed using CellRanger and analyzed using the R package Seurat. In addition, FFPE slides from each tumor that underwent scRNAseq were requested and analyzed using multiplexed immunohistochemistry (VECTRA platform) for CD45, CD20, CD8, CD4, Foxp3, CD68 and DAPI. Slides were scanned and unmixed using inForm and Phenochart software.

Results: To date, eleven patients with primary (four) or relapsed (seven) osteosarcoma or Ewing sarcoma tumors and paired peripheral blood have been analyzed to date. Use of fresh tissue specimens currently limits this work to our local institution. scRNAseq reveals distinct clustering of CD8+ cells between tumor infiltrating leukocytes, patient-matched peripheral blood and the "normal" age-matched peripheral blood cohort. CD8+ cells infiltrating relapsed Ewing sarcoma demonstrate an effector/cytotoxic T-cell signature. Ewing sarcoma and osteosarcoma CD8+ profiles are distinct. Myeloid cell population analysis revealed distinct differences between tumor versus peripheral blood populations and between primary versus recurrent tumors. Multiplexed immunohistochemistry analysis confirmed the presence and clustering of immune cell populations within the tumor tissue specimen.

Conclusion: scRNAseq on fresh bone sarcoma samples and paired patient peripheral blood is feasible and suggests unique differences exist between the immune microenvironments of primary versus relapsed specimens. Ongoing studies continue to expand this cohort and compare results to viably frozen specimens. These data expand the detailed knowledge of bone sarcoma microenvironment and provide a reference dataset for future studies determining how therapeutic interventions may alter baseline immune signatures.

Paper #11 3446540

PULMONARY MICRONODULES LESS THAN 5 MM DETECTED ON CT AT PRESENTATION IN PATIENTS WITH OSTEOSARCOMA DO NOT EFFECT 5 YEAR OVERALL SURVIVAL

Reid Davison[1], *Fadi Hamati*[1], *Paul Kent*[1]
[1]*Rush Medical Hospital, Chicago, Illinois, UNITED STATES*

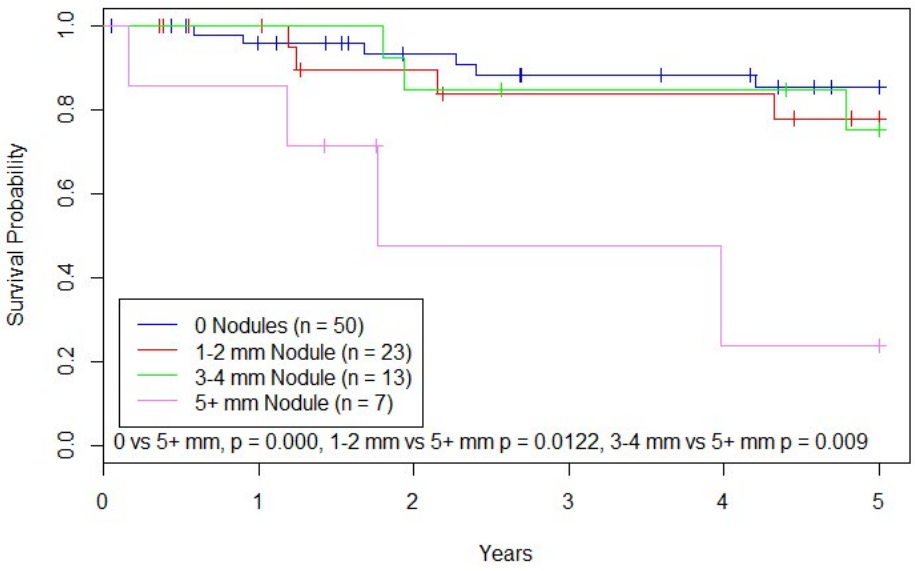
Objective: The wide spread adoption of high resolution CT scans in the last 25 years have revealed pulmonary micronodules not previously seen and surgical recommendations have not recently changed to reflect this reality, therefore our objective is to study the relationship between size and location of lung micronodules discovered on CT at the time of diagnosis of osteosarcoma (OST) and overall 5 year overall survival to aid in the revision of surgical guidelines.

Methods: We retrospectively collected data on all newly diagnosed OST patients, age less than 50, treated at Rush University Hospital over 25 years from 1995-2020 who had an initial CT chest within 1 month of diagnosis. Lesions were counted as micronodules if they were not explicitly defined as benign, if they were surrounded by lung parenchyma, and if they were ≤ 8 mm. Size, location of nodules, and if they were resected, was recorded. Additionally, dates of last known alive and dates of death were recorded. Kaplan Meier curves, Tarone-Ware tests, t tests, and 1 and 2 way ANOVAS, were run using RStudio.

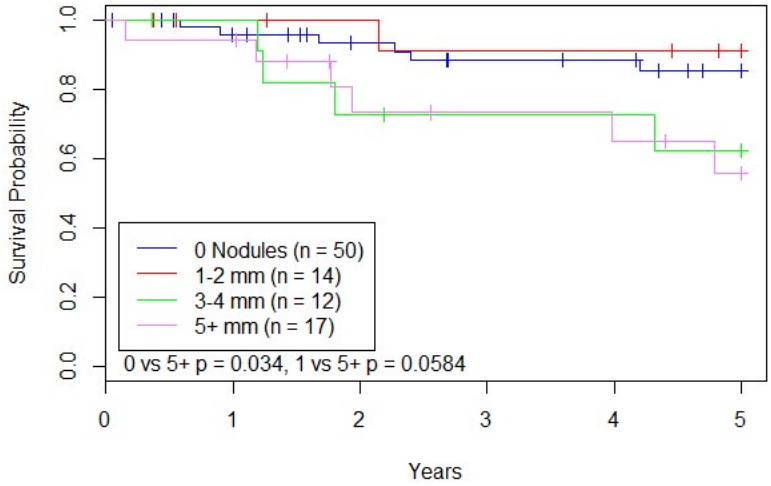
Results: Over 25 years, there were 93 patients (mean age = 21, range = 6-48, 40F, 53M) that fit our inclusion and exclusion criteria. 43 (46.2%) patients had nodules on presentation and 50 did not. Of the 67 patients who we had conformation at 5 years if they were alive or dead, 52 were still alive (78%). On presentation, 4 patients had a 1 mm nodule, 19 patients had a 2 mm nodule, 8 had a 3 mm nodule, 5 had a 4 mm nodule, 2 had a 5 mm nodule, 2 had a 6 mm nodule, and 3 had 8 mm nodules. Only one patient had a lung surgery immediately after identifying nodules (6 nodules, largest 8 mm) on CT at presentation. Kaplan-Meier curve comparing 5 year overall survival of patients with their largest nodules on presentation at each size interval showed there was no difference in 5 year overall survival in patients with any size nodule less than 5 mm compared to patients with no nodules (figure 1). Also those who presented with nodules ≥5 mm had a significantly shorter 5 year overall survival than those who had no nodules, nodules 1-2 mm, or nodules 3-4 mm in diameter (figure 1). However, if patients whose largest nodule was ≥4 mm were compared with patients with 0 nodules and those whose largest nodule was 1, 2, or 3 mm, there is no significant difference in 5 year overall survival (data not shown). Additional analysis of micronodule size involved adding up the sizes of nodules for patients with more than one nodule (ex, 3mm and 4 mm nodules represented as 7 mm). Patients with any additive nodule size less than 5 mm did not effect 5 year overall survival (figure 2). Lastly, the number of lobes involved was analyzed. Figure 3 indicates that patients with 2 or more lobes involved, regardless of laterality, have worse 5 year life expectancies than those who presented with 0 or 1 lobe involvement.

Conclusion: Our retrospective, single institution study of 93 patients showed no difference in 5 year overall survival for those who presented with any number of nodules less than 5 mm in size, or for patients with an additive nodule size less than 5 mm, compared to having no nodules. Additionally, there was no difference in 5 year overall survival for those who presented with 1 lobe involved in comparison to having no nodules. Standard practice has been to remove all visible nodules, however, these recommendations have existed for 25 years, before high resolution CT showed nodules less than 3 mm. Our data suggest surgery is not necessary for nodules less than 5 mm identified on presentation.

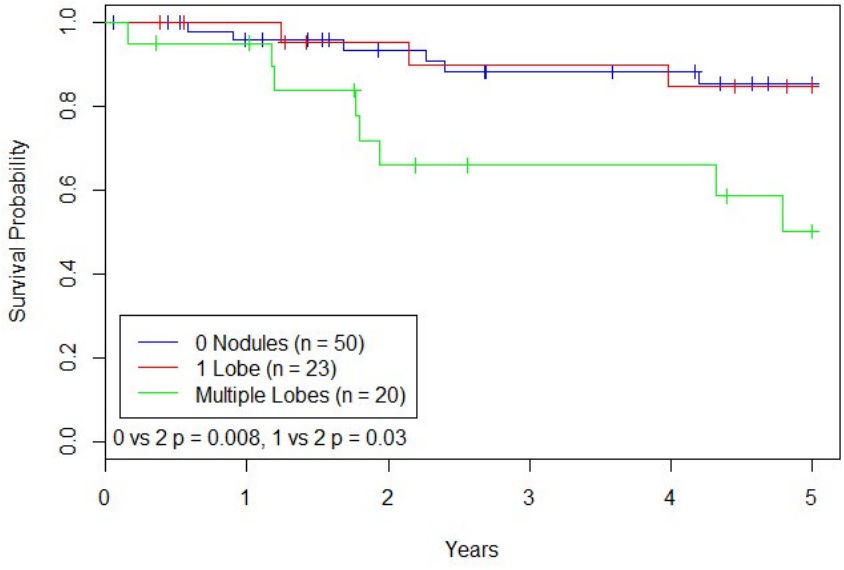
Kaplan-Meier Curve: Size of Largest Nodule on Presentation



Kaplan-Meier Curve: Additive Nodule Size



Kaplan-Meier Curve: Number of Lobes Involved on Presentation



Paper #12 3461610

TARGETING MASTER REGULATOR DEPENDENCIES IN PEDIATRIC OSTEOSARCOMA

Jovana Pavisic[1], *Katherine Janeway*[2], *Andrew Kung*[3], *Filemon Dela Cruz*[3], *Alejandro Sweet-Cordero*[5], *Inge Behroozfard*[5], *Stanley Leung*[5], *Alex Lee*[5], *Darrell Yamashiro*[1], *Julia Glade Bender*[3], *Andrea Califano*[4]
[1]*Pediatrics, Columbia University Irving Medical Center, New York, New York, UNITED STATES;* [2]*Pediatrics, Dana-Farber/ Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts, UNITED STATES;* [3]*Pediatrics, Memorial Sloan Kettering Cancer Center, New York, New York, UNITED STATES;* [4]*Systems Biology, Columbia University Irving Medical Center, New York, New York, UNITED STATES;* [5]*Pediatrics, University of California San Francisco, San Francisco, California, UNITED STATES*

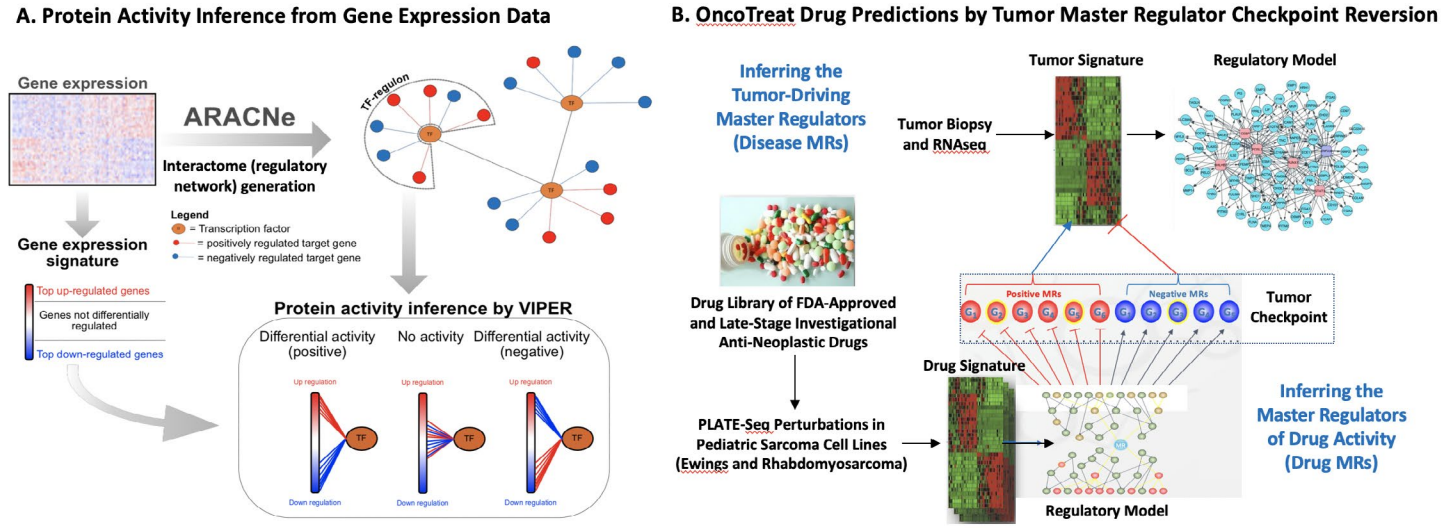
Objective: Outcomes in pediatric osteosarcoma (OS) remain poor, particularly for those with primary metastatic or relapsed disease. Mutation-based precision oncology approaches are limited due to lack of targetable mutations and significant genetic heterogeneity. We leveraged established network-based systems biology approaches to discover common targetable disease drivers—master regulator (MR) proteins—in OS to expand molecularly-based rational therapy selection.

Methods: Using metaVIPER (Virtual Inference of Protein Activity by Enriched Regulon Analysis), we interrogated tissue-matching cancer gene regulatory networks with 160 clinically-annotated OS gene expression samples to infer tumor-specific protein activity based on enrichment of the protein's transcriptional targets in the tumor's differential gene expression signature (Fig 1A). We obtained RNAseq profiles from drug perturbations using the PLATEseq technology and a 450-compound library of FDA-approved and late-stage investigational anti-neoplastic drugs performed in two pediatric sarcoma cell lines selected based on their ability to recapitulate patient MR protein signatures by enrichment analysis. VIPER was used to infer protein activity before and after drug treatment in each cell line, and this data was used via the OncoTreat algorithm to prioritize effective drugs in the 160 OS samples by their ability to reverse the patient-specific MR-activity signatures and shut off the tumor's transcriptional program (Fig 1B). We performed unsupervised clustering using the partition around medoids algorithm to define OS subtypes with common MR signatures and predicted drug sensitivities. We suggest clinically-relevant drugs that showed the most significant reversal of patient MR signatures in distinct groups of patients for further *in vivo* testing.

Results: Despite underlying genetic heterogeneity, patients with OS cluster into two groups based on MR protein activity (Fig 2). Differential protein activity was seen in proteins involved in epigenetic modification (CHD9, ATRX, ASXL2, MBD3), chemotherapy sensitivity (STUB1, PHB, RUVBL2), and tumor metabolism and aggressiveness (SIRT6, SIVA1). Evaluating directly targetable MRs, we identified distinct groups of patients with aberrant activation of: a) matrix metalloproteases, LOXL2, and PDGFRB; b) PIK3CA and XPO1; c) HDACs; and d) TOP2A, CDK1, RRM2, and EZH2. These proteins have been previously successfully targeted with many agents available for pediatric patients. Patients further clustered by OncoTreat-predicted drug sensitivities with the two MR clusters representing unique pharmacotypes (Fig 3). Notably, no drug was predicted to be effective in a majority of patients. Rather, multiple drugs currently under investigation in pediatric tumors including OS, showed significant predicted activity (p-value < 0.00001) in small subgroups of patients. One group of patients (24%) showed high sensitivity to Decitabine, which is regularly used in pediatric patients and has shown experimental efficacy in OS as a demethylating agent. Other groups of patients showed high sensitivity to drugs currently in trials for pediatric sarcoma, including Lenvatinib (17%), Neratinib (15%), Entinostat (15%), and Pazopanib (12%), providing computational evidence for further testing of these agents in basket trials.

Conclusion: Using innovative computational algorithms and pediatric OS gene expression data, we find that two MR subtypes recapitulate the regulatory landscape in OS and show association with predicted drug sensitivities. We identify multiple subsets of patients with aberrant activation of targetable MR proteins and predicted MR-reversing drugs sensitivities, and suggest that basket trials with MR-based therapy prediction may be a more effective approach in OS. We will refine this analysis using emerging data from OS-specific cell lines replicating the common OS MR signatures to optimize OncoTreat-therapy prioritization and will validate findings in molecularly-matched PDX models.

Figure 1. Methods review. **A.** metaVIPER performs an integrative analysis of ARACNe-generated cancer regulatory networks to infer the activity of ~6,000 potential MR proteins in individual tumors based on the differential expression of the protein's targets in the tumor's gene expression signature. It has been shown that tumors maintain their malignant transcriptional state through genetically-induced, aberrant activation of a few MR proteins (tumor checkpoint). Tumor checkpoints represent more universal dependencies as they integrate the effects of a large number of genetic alterations. **B.** metaVIPER can be used to infer the activity of directly targetable disease-driving MR proteins (OncoTarget). The OncoTreat algorithm additionally prioritizes FDA-approved or late-stage investigational drugs by their ability to induce tumor checkpoint collapse in individual tumor samples based on the drug's differential MR signature computed from drug perturbations performed in matched cell lines.



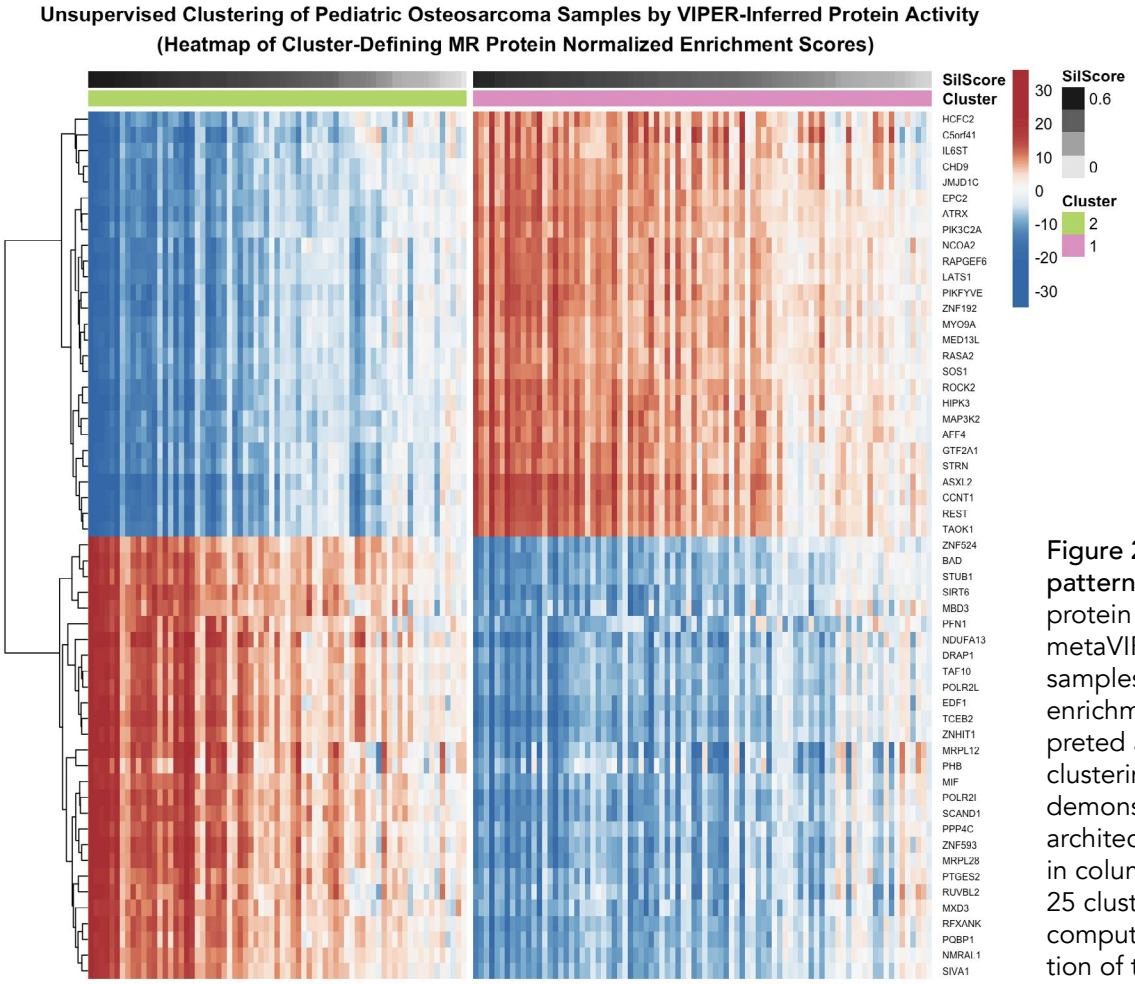
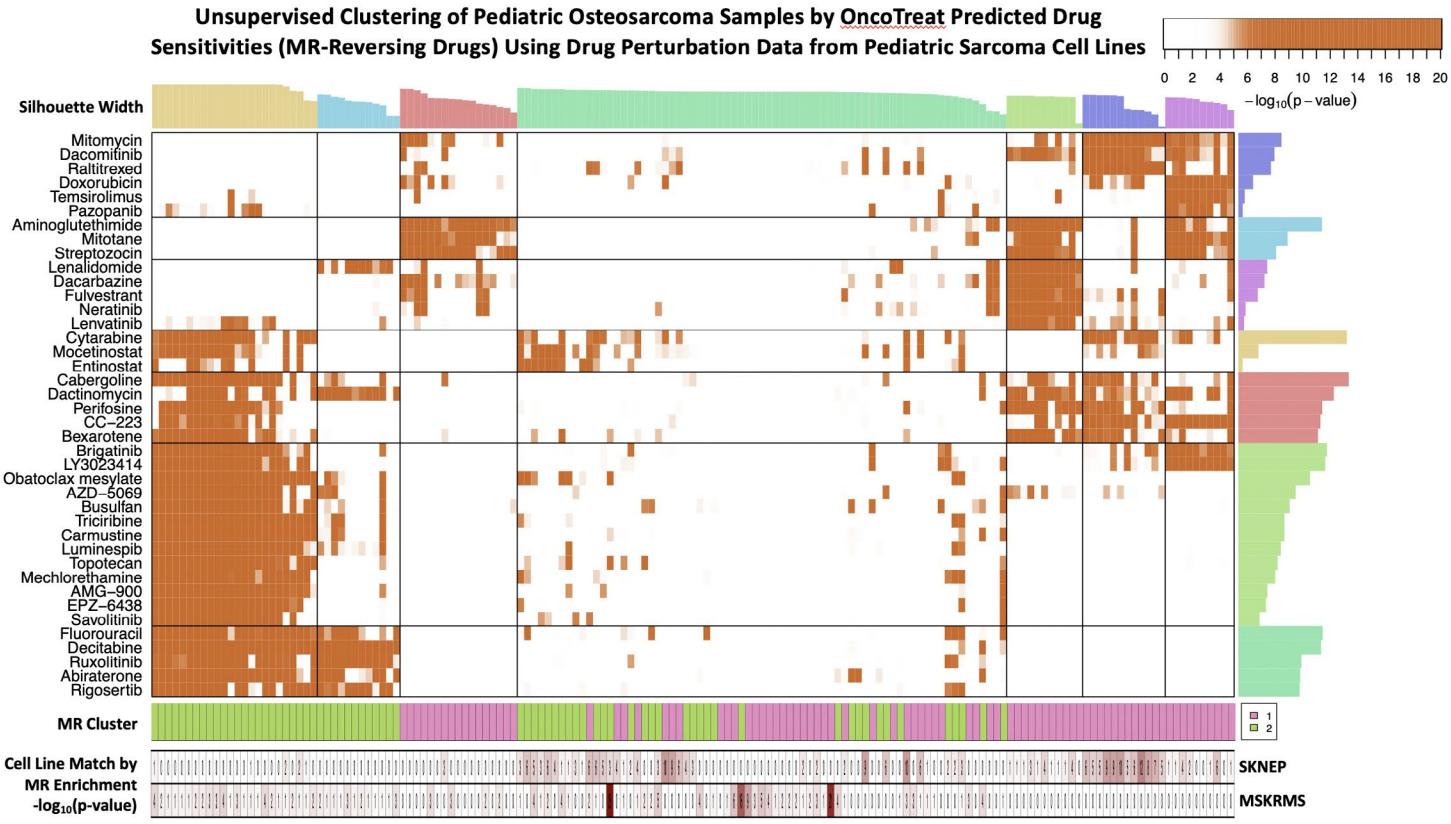


Figure 2. Master regulator patterns in OS. Heatmap of MR protein activity computed by metaVIPER in 160 pediatric OS samples, reported as normalized enrichment scores (NES) interpreted as z-scores. Unsupervised clustering by MR protein activity demonstrated 2 dominant MR architectures. Patient tumors are in columns and the top/bottom 25 cluster-defining MR proteins computed by Stouffer integration of the NES in rows.

Figure 3. OncoTreat drug prioritization. Drugs were prioritized based on their ability to revert the activity of the top 50 most aberrantly active MR proteins in each of the 160 OS tumor samples using drug-induced differential MR signatures generated in the context of two pediatric sarcoma cell lines (Ewing sarcoma - SKNEP and Rhabdomyosarcoma - MSKRMS-12808). Patient tumors are in columns and drugs in rows. Tumors form distinct clusters of predicted drug sensitivities (pharmacotypes) that segregate with the two dominant MR clusters. Drug MR-reversal scores were weighted by the cell line match between each patient sample and the two cell lines computed by enrichment of the patient's most aberrantly active MRs in the cell line's MR signature.



9:00 am - 10:00 am – Session 6 –

CHONDROSARCOMA, CHORDOMA, AND OTHER BONE TUMORS

Paper #13 3465391

BEYOND THE INFLUENCE OF IDH MUTATIONS: EXPLORING EPIGENETIC VULNERABILITIES IN CHONDROSARCOMA

Sanne Venneker[1], *Alwine B. Kruisselbrink*[1], *Zuzanna Baranski*[2], *Ieva Palubeckaite*[1], *Inge H. Briaire-de Bruijn*[1], *Jan Oosting*[1], *Pim J. French*[3], *Erik Danen*[2], *Judith V. Bovee*[1]
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Objective: Chondrosarcomas are malignant cartilage producing tumours for which surgical resection remains currently the only treatment option due to the high intrinsic chemo- and radiotherapy resistance and the lack of targeted therapeutic options. Both enchondromas and chondrosarcomas frequently harbour hotspot mutations in isocitrate dehydrogenase (*IDH1* or *IDH2*), leading to elevated levels of the oncometabolite D-2-hydroxyglutarate (D-2-HG) which causes widespread changes in the epigenetic landscape of these tumours. *IDH* mutant enchondromas are characterized by a CpG island methylator phenotype (CIMP)-positive status and a hypermethylation phenotype is observed in high-grade *IDH* mutant chondrosarcomas, suggesting that targeting of the epigenetic landscape might be beneficial for chondrosarcoma patients. Therefore, the aim of this study was to explore whether the methylome of *IDH* mutant cartilaginous tumours changes upon progression from benign/low-grade cartilage tumours to high-grade chondrosarcoma and if these underlying epigenetic vulnerabilities could be used as a therapeutic target for chondrosarcoma.

Methods: A DNA methylation array was performed on fresh-frozen benign, low-grade or high-grade *IDH* mutant cartilage tumour samples (n=21). The data was used to explore if the CIMP-status was retained upon tumour progression and to identify differentially methylated genes between low-grade and high-grade samples. The online pathway analysis tools PANTHER and DAVID were used to identify enriched pathways in the differentially methylated gene sets. Subsequently, a broad epigenetic compound screen containing 128 compounds targeting different epigenetic key players (e.g. histone deacetylases (HDACs), histone methyltransferases (HMTs), and DNA methyltransferases (DNMTs)) was performed on *IDH* wild type and mutant chondrosarcoma cell lines (n=5). For one of the most promising hits, the HDAC inhibitor romidepsin, dose-response curves were performed in both 2D (n=10) and 3D *in vitro* models of chondrosarcoma (n=3). Furthermore, RNA expression of HDAC subtypes was assessed and the underlying cell death mechanism of romidepsin was explored. Additionally, several combination therapies with non-epigenetic drugs (e.g. chemotherapy, BCL2 family member inhibitors and glutaminolysis inhibitors) were investigated to assess if HDAC inhibition could be used in combination therapies to enhance sensitivity towards non-epigenetic therapies.

Results: The CIMP-positive status is retained upon progression from benign/low-grade *IDH* mutant cartilage tumours to high-grade chondrosarcoma. In fact, high-grade tumours showed an overall increase in the number of highly methylated genes, indicating that the DNA methylation pattern changes upon tumour progression. However, no enriched pathways were identified in the differentially methylated gene sets, suggesting a more wide-spread phenomenon. The broad epigenetic compound screen showed that chondrosarcomas are highly sensitive to HDAC inhibition in both 2D and 3D *in vitro* models, independent of the *IDH* mutation status or the chondrosarcoma subtype. Class I HDAC subtypes seem to play the most prominent role in chondrosarcoma and are likely to underlie HDAC inhibitor sensitivity. Romidepsin, an HDAC1 and HDAC2 inhibitor, sensitized chondrosarcoma cell lines to glutaminolysis and BCL2 family member inhibitors, which suggests that HDAC enzymes define the metabolic state and apoptotic threshold of chondrosarcoma.

Conclusion: Taken together, the chondrosarcoma methylome changes upon tumour progression, and an increased number of methylated genes is associated with aggressiveness of the disease. This study shows that HDAC enzymes play a prominent role in the epigenetic landscape and survival of chondrosarcoma cells, especially class I HDACs. Therefore, inhibition of HDAC enzymes seems a promising targeted therapeutic strategy for chondrosarcoma patients, either as monotherapy or as part of combination strategies.

Paper #14 3442269

OUTCOME IN DEDIFFERENTIATED CHONDROSAROMA FOR PATIENTS TREATED WITH MULTIMODAL THERAPY: RESULTS FROM THE EURO-B.O.S.S STUDY

Ivar Hompland[1], *Stefano Ferrari*[2], *Stefan Bielack*[3], *Emanuela Palmerini*[2], *Kirsten S. Hall*[1], *Davide M. Donati*[2], *Elisabetta Setola*[2], *Virginia Ferraresi*[4], *Rossella Bertulli*[9], *Alessandro Comandone*[5], *Pierro Picci*[1], *Stefanie Hecker-Nolting*[3], *Claudia Blattmann*[3], *Leo Kager*[7], *Thomas Kühne*[6], *Peter Reichardt*[8], *Sigbjørn Smeland*[1]

[1]*Department of Oncology, Oslo University Hospital, Norwegian Radium Hospital, Oslo, NORWAY;* [2]*Oncology Department, Istituto Ortopedico Rizzoli, Bologna, ITALY;* [3]*Stuttgart Cancer Center, Pediatrics 5 (Oncology, Hematology, Immunology), Klinikum Stuttgart Olgahospital, Stuttgart, GERMANY;* [4]*Oncology Department, Istituto Regina Elena, Rome, ITALY;* [5]*Oncology Department, Ospedale Humanitas-Gradenigo, Turin, ITALY;* [6]*Division of Oncology and Hematology, University Children's Hospital, Basel, SWITZERLAND;* [7]*Department of Pediatrics, St Anna Children's Hospital, Medical University Vienna, Vienna, AUSTRIA;* [8]*Department of Oncology, Helios Klinikum Berlin-Buch, Berlin, GERMANY;* [9]*Oncology Department, Istituto Nazionale Tumori, Milan, ITALY*

Objective: EUROpean Bone Over 40 Sarcoma Study (EURO–B.O.S.S) was a collaboration between the Italian, COSS (Germany, Switzerland, Hungary and Austria) and Scandinavian sarcoma groups that aimed to report activity and toxicity of chemotherapy added to surgery in patients aged over 40 with osteosarcoma and other spindle cell sarcomas. An aged modified osteosarcoma chemotherapy regimen was given to all patients regardless the histology. The effect of adding systemic chemotherapy to the surgical treatment of patients with dedifferentiated chondrosarcoma (DDCS) is still under discussion. Here, we present the outcome in the subgroup of patients with DDCS.

Methods: Fifty-seven patients with DDCS (localized, 34 [60%]; metastatic, 23 [40%]) were included. The chemotherapy regimen was based on doxorubicin, ifosfamide, cisplatin, and post-operative methotrexate in case of poor histological response (> 50 % viable cells). Toxicity was graded according to the National Cancer Institute expanded common toxicity criteria, version 2.0 and survival was analyzed using Kaplan–Meier curves, log-rank tests, and univariate Cox regression models.

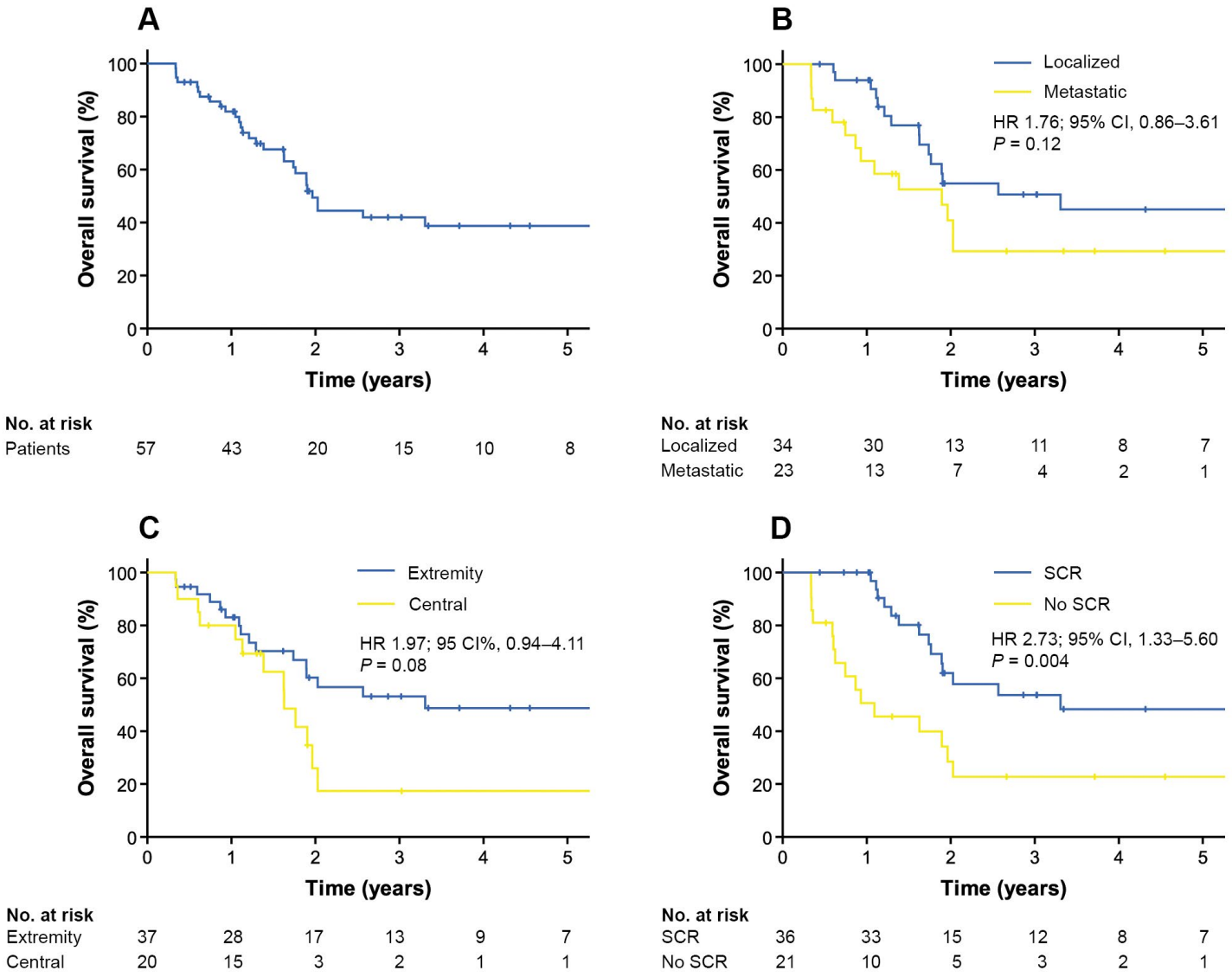
Results: There were 23 males and 34 females, and the median age was 52 years (range, 42–65). The majority of the primary tumors were located in extremities (37 patients; 65%), while the remaining had central tumors. Thirty-five patients (59%) had localized disease, while the rest (41%) had metastatic disease at primary diagnosis. Fifty-four of 57 patients underwent surgical resection of the primary tumor; of whom, 34 (58%) patients underwent primary resection and 22 (37%) after neoadjuvant chemotherapy. Complete surgical removal of all clinically detectable tumor sites (primary tumor and all metastases, if metastatic disease) was attempted. Surgical complete remission (SCR) was achieved in 36 (63%) patients.

The median follow-up time was 20 months (range, 4–128) for all patients and 40 months (range, 5–128) for not deceased patients. For the whole cohort, the median OS was 24 months (95% confidence interval [CI], 22–25) and the 5-year survival was 39% (Figure 1A). At the end of follow-up, 27 patients were still alive; 13 patients had no evidence of disease (NED), 4 had NED after a second complete surgery, and 10 were alive with disease. Thirty patients died due to chondrosarcoma. Comparing extremity localization to central localization, patients with extremity localization had a 5-year OS of 49% vs. 29% for non-extremity localization (hazard ratio [HR] 1.97; 95 CI%, 0.94–4.11; $P = 0.08$; Figure 1B). Patients with localized disease had a five-year OS of 46% compared 29 % for patients with primary metastatic disease (HR 1.76; 95% CI, 0.86–3.61; $P = 0.12$; Figure 1C). For patients in SCR, the 5-year OS was 49% compared to 23% for patients that did not obtain SCR (HR 2.73; 95% CI, 1.33–5.60; $P = 0.004$; Figure 1D). Univariate analysis showed that only SCR was statistically significant for better OS. Due to the small patient number, a multivariable analysis was not performed.

When analyzing the 36 patients that obtained SCR, 22 (59) patients had relapse; 15 had a distant relapse, five had a local relapse, and two had a combination. Most patients with a distant relapse had lung metastases (14 patients, 82%). The median MFS was 25 months (95% CI, 21-28) and 5-year MFS was 32%.

The chemotherapy toxicity was considerable but manageable. There were no treatment related death and 39 (70 %) patients received ≥ 6 cycles of the planned nine chemotherapy cycles.

Conclusion: Adding chemotherapy to surgery improves the estimated 5-year OS of DDCS compared to data from previously reported retrospective studies and should be considered in the management of patients aged > 40 year.



Kaplan-Meyer survival curves. A) For the complete cohort; B) Stratified according to disease status; C) Stratified according to location of the primary tumor; D) Stratified according to surgical complete remission (SCR) or not.

Paper #15 3461741

DEFINITIVE HIGH-DOSE, PROTON-BASED RADIATION FOR UNRESECTED MOBILE SPINE AND SACRAL CHORDOMAS

Thomas F. DeLaney[1], *Norbert J. Liebsch*[1], *Saveli Goldberg*[1], *Walter H. Banfield*[2], *Myrsini Ioakeim-Ioannidou*[1], *Soha Ahmed*[3], *Joseph H. Schwab*[4], *Francis J. Hornicek*[7], *Gregory M. Cote*[5], *John H. Shin*[6], *Edwin Choy*[5], *Yen-Lin E. Chen*[1]
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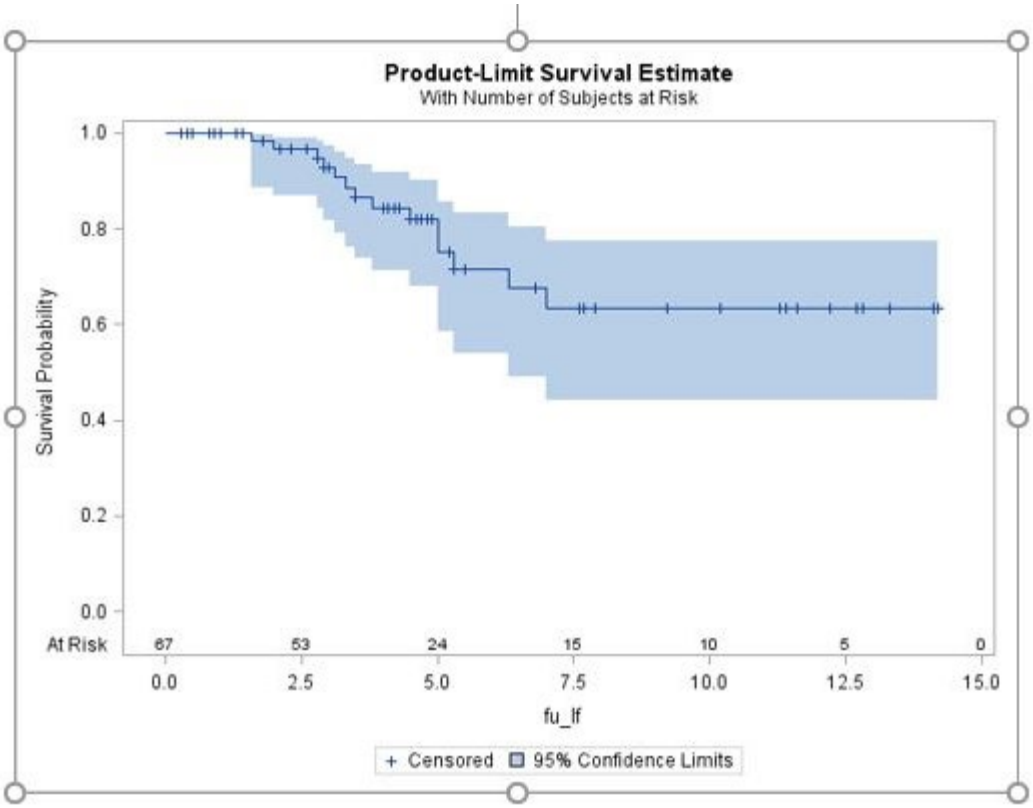
Objective: Spine chordoma is treated primarily by surgical resection. However, the local recurrence rate is high. Adjuvant radiotherapy to adequate dose improves local control (LC). In certain locations, such as high sacrum, resection may result in significant neurological dysfunction, so definitive radiation has been used as an alternative to surgery. The purpose of this study is to report the results of high-dose, proton-based definitive radiotherapy for unresected spinal and sacral chordomas.

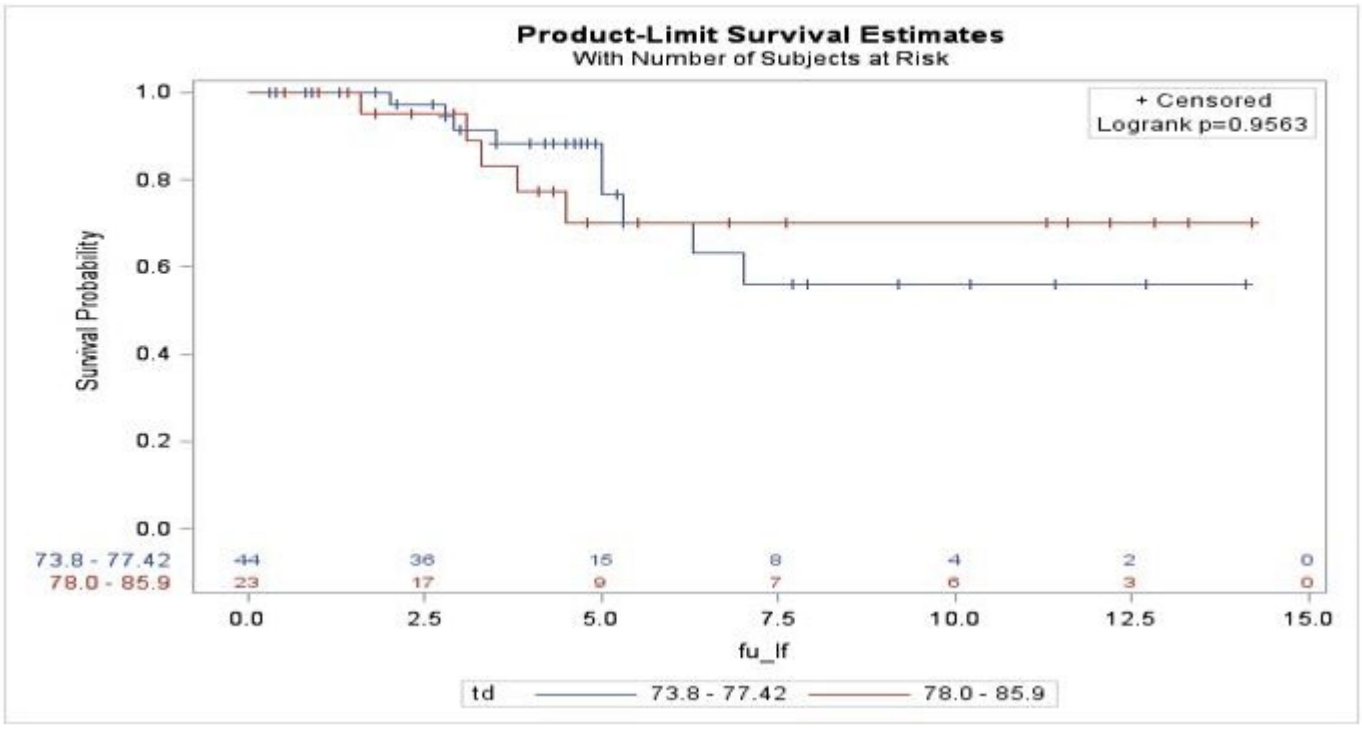
Methods: We retrospectively reviewed 67 patients with newly diagnosed, previously untreated spinal chordomas (biopsy only; no prior resection) treated with high-dose definitive, proton-based radiotherapy at our center from 1975 to 2019. Reasons for radiotherapy alone included medical inoperability and/or concern for neurological dysfunction based on spine level or patient choice.

Results: Median age at diagnosis was 67.1 years. Male 53.7 %; female 46.3%. Tumor locations included cervical (n=10), thoracic (n=1), lumbar (n=4) spine, and sacrum (n=52). Median maximal tumor diameter was 7.4 cm (range 1.8- 25 cm). Most patients were irradiated in daily fraction sizes of 1.8-2 GyRBE, although some patients were irradiated with daily doses as high as 2.5 GyRBE per fraction, so doses were normalized to daily dose of 1.8 GyRBE daily (using an alpha/beta ratio of 3). Median total dose was 77.4 GyRBE. Analysis with median follow-up of 56.2 months (maximum 14.3 years) showed overall survival of 83.5% (95%CI:69.4-91.5%) and 65.6% (95%CI: 46.7-79.1%), chordoma-free survival of 56.4% (95%CI: 40.8 – 69.4) and 42.7% (95%CI: 26.6 – 57.8%), local control of 81.9% (95%CI: 67.8-90.2%) and 63.3% (95%CI: 44.3 – 77.4%), and distant control of 75.0% (95%CI: 60.4-84.8%) and 70.3%(95%CI: 53.2 – 82.1%) at 5 and 8 years respectively. In Cox model for local control (Likelihood Ratio Statistic), total dose: HR 0.85 (95%CI: 0.63-1.06), p=0.174. LC at 8 years with dose= 73.8-77.42 GyRBE was 56.2% (95%CI: 30.1-75.9) compared to 70.2% (95%CI: 42.0-86.5) with 78.0-85.9 GyRBE, p=0.956. In Cox model for distant control, size: HR 1.07 (95%CI: 0.98-1.15), p=0.104 and sacral site showed a trend, HR:3.75 (95% CI:0.75-66.7) p=0.121. Distant control for tumors <= 7.4 cm at 8 years was 79.3% (95%CI: 56.6-91.0%) compared to only 60.3% (95%CI: 33.5-79.2%) for tumors > 7.4 cm, p=0.277. Distant control at 8 years for sacral tumors was 65.9% (95%CI: 46.7-79.6%) vs. 88.9% (95%CI: 43.3- 98.4%) for other sites, p=0.169. Late side effects included insufficiency fracture (n=15, 22.4%), proctitis/ rectal bleeding (n=4, 6.0%), spinal or sacral nerve Injury (n=5, 5.5%), soft tissue fibrosis (n=1, 1.5%), and infection (n=1, 1.5%). Rate of any late complication was 37.0%(95%CI: 25.7-51.3%) at 5 years and 44.9%(31.3-61.2%) at 8 years. In Cox model for complications (Likelihood Ratio Statistic), there was no clear relationship to total dose: HR 0.97(95%CI:0.79-1.14) p=0.707.

Conclusion: These data support the use of high-dose definitive radiotherapy for patients with medically inoperable or otherwise unresected mobile spine or sacrococcygeal chordomas. Local control, however, continues to be a challenge in this patient population, with ongoing local recurrences after 5 years. There is a trend towards better local control with high doses. There is a trend towards higher rates of metastatic disease with large and sacral tumors.



Local Control: Doses



Paper #16 3463234

RESULTS FROM THE CHONDROSARCOMA PHASE 1 STUDY EXPANSION COHORT OF THE TETRAVALENT DEATH RECEPTOR 5 AGONIST INBRX-109

Sant P. Chawla[1], *Nehal Lakhani*[4], *Anthony Tolcher*[5], *Christopher Lieu*[3], *Breelyn A. Wilky*[3], *Klaus W. Wagner*[2], *Analeah Heidt*[2], *Brendan Eckelman*[2], *Quinn Deveraux*[2], *James Kalabus*[2], *Anthony P. Conley*[6], *Vivek Subbiah*[6]
[1]*Sarcoma Oncology Center, Santa Monica, California, UNITED STATES;* [2]*Inhibrx, Inc, La Jolla, California, UNITED STATES;* [3]*University of Colorado, Aurora, Colorado, UNITED STATES;* [4]*START Midwest, Grand Rapids, Michigan, UNITED STATES;* [5]*NEXT Oncology, San Antonio, Texas, UNITED STATES;* [6]*MD Anderson Cancer Center, Houston, Texas, UNITED STATES*

Objective: INBRX-109 is a precisely engineered single domain antibody-based therapeutic targeting death receptor 5 (DR5). DR5 agonism leads to apoptosis or programmed cell death. Although expressed throughout the body, cancer cells are inherently more sensitive to DR5 signaling than healthy tissues, which has inspired a variety of clinical approaches to target this receptor. The tetravalent nature of INBRX-109 was empirically selected to overcome the limitations of agents with alternate valencies, either lack of efficacy or hepatoxicity, and maximize the therapeutic index of DR5 activation. In preclinical studies, INBRX-109 potently agonizes DR5 and induces cancer cell death through efficient receptor clustering, without effecting primary human hepatocytes or HepaRG hepatic cells. We have observed preclinical activity of INBRX-109 in many human cancer types including sarcoma, mesothelioma, gastric cancer, colorectal cancer, pancreatic cancer, and non-small cell lung cancer. Chondrosarcoma was prioritized as an expansion cohort for this first-in-human Phase 1 study, based on the observation of early signs of clinical activity in this sarcoma subtype with previous bi- and trivalent anti-DR5 therapeutics.

Methods: The traditional 3+3 dose escalation part of the Phase 1 study of INBRX-109 (NCT03715933) was completed in August 2019. INBRX-109 was well-tolerated in 20 patients, with no significant toxicities observed at doses up to and including the maximum administered dose of 30 mg/kg. No MTD was reached. In the expansion cohorts, patients with distinct tumor types, including chondrosarcoma, will be evaluated for safety, PK, immunogenicity and efficacy of INBRX-109.

Results: As of 24 June 2020, we have treated 11 chondrosarcoma patients, with unresectable or metastatic disease, with INBRX-109 (3 mg/kg, N=10; or 10 mg/kg, N=1) IV on day 1 of 21-day cycles. The median age was 56 and 82% of patients were male. INBRX-109 was well-tolerated without unexpected toxicities and low incidence of ≥ Grade 3 adverse events (AE) or serious AE (SAE).

We observed signs of single agent efficacy, durable partial response (PR) and stable disease (SD), in patients with chondrosarcoma, as summarized in the swimmer plot in Figure 1. One patient achieved a PR with 55% percent reduction of the sum of target lesions by RECISTv1.1 (Figure 2.), 6 out of 8 patients (75%) had SD as best response, disease control rate (SD+PR) was 87.5% (7 out of 8 patients), and 1 patient had SD with PFS of approximately 8 months (prior lines of therapy: best response progressive disease after 4 months on pazopanib, and SD for 3 months on pembrolizumab). Six patients are continuing on study and 3 patients are pending their first tumor assessments. The study is ongoing and we are planning to present updated safety, PK, immunogenicity and efficacy data of single agent INBRX-109 in chondrosarcoma patients.

Conclusion: In chondrosarcoma patients INBRX-109 shows evidence of single agent efficacy with durable partial response and stable disease supporting further clinical investigation.

Figure 1. Efficacy of INBRX-109 in Chondrosarcoma Patients

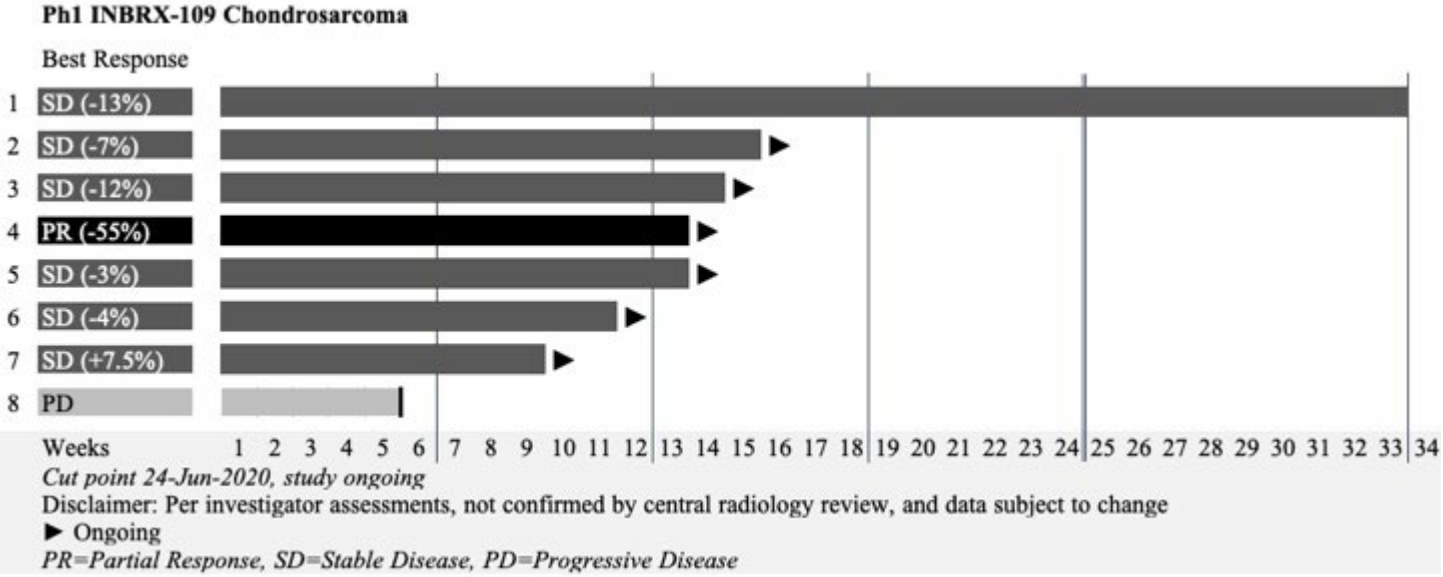
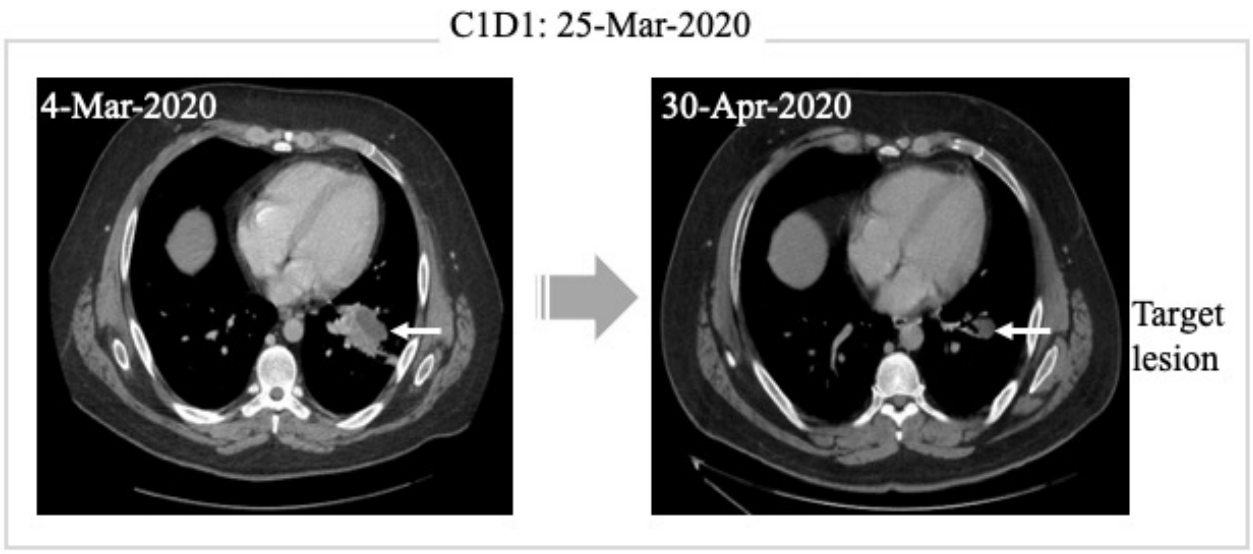


Figure 2. Example of Partial Response of INBRX-109



10:30 am - 11:30 am

– Session 7 –

LIPOSARCOMA

Paper #17 3464763

PREOPERATIVE RADIOTHERAPY IN PATIENTS WITH PRIMARY RETROPERITONEAL SARCOMA (RPS): TRIAL (STRASS) VS OFF-TRIAL (STREXIT) RESULTS

Dario Callegaro[1], *Chandrajit Raut*[12], *Ajayi Taiwo*[2], *Dirk Strauss*[3], *Sylvie Bonvalot*[4], *Deanna Ng*[5], *Eberhard Stoeckle*[6], *Mark Fairweather*[12], *Piotr Rutkowski*[7], *Winan J. van Houdt*[8], *Hans Gelderblom*[9], *Claudia Sangalli*[13], *Andrew Hayes*[3], *Charles Honoré*[10], *Rebecca Gladdy*[5], *Magali Fau*[6], *Rick L. Haas*[11], *Dmitri Tzanis*[4], *Aisha B. Miah*[14], *Peter Chung*[15], *Elizabeth H. Baldini*[16], *Sandrine Marreaud*[2], *Saskia Litière*[2], *Carol J. Swallow*[5], *Alessandro Gronchi*[1]
[1]*Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, ITALY;* [2]*EORTC Headquarters, Brussels, BELGIUM;* [3]*General Surgery, Sarcoma Unit, Royal Marsden NHS Foundation Trust, London, UNITED KINGDOM;* [4]*Surgery, Institut Curie, Paris, FRANCE;* [5]*Surgical Oncology, Princess Margaret Cancer Centre/Mount Sinai Hospital, University of Toronto, Toronto, Ontario, CANADA;* [6]*Surgery, Institut Bergonié, Bordeaux, FRANCE;* [7]*Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, POLAND;* [8]*Surgery, The Netherlands Cancer Institute, Amsterdam, NETHERLANDS;* [9]*Medical Oncology, Leiden University Medical Center, Leiden, NETHERLANDS;* [10]*Surgery, Institute Gustave Roussy, Villejuif, FRANCE;* [11]*Radiation Oncology, The Netherland Cancer Institute, Amsterdam, NETHERLANDS;* [12]*Surgery, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, UNITED STATES;* [13]*Radiation Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, ITALY;* [14]*Radiation Oncology, Royal Marsden NHS Foundation Trust, London, UK, London, UNITED KINGDOM;* [15]*Radiation Oncology, Princess Margaret Cancer Centre/Mount Sinai Hospital, Toronto, Ontario, CANADA;* [16]*Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, UNITED STATES*

Objective: To compare the outcome of patients with primary RPS treated within (STRASS cohort) or outside (STREXIT cohort) of the EORTC 62092-22092 (STRASS) phase III trial of preoperative radiotherapy (RT) + surgery vs surgery alone. We also aimed to assess the effect of RT administration on oncological outcomes in the STREXIT cohort and in a pooled STRASS + STREXIT cohort.

Methods: Patients included in the STRASS trial formed the STRASS cohort. All consecutive adult patients with primary RPS who underwent surgery among 10 European and North American STRASS centers between Jan 2012 and Apr 2017 (STRASS recruiting period) and not enrolled in STRASS were included in the STREXIT cohort. Study end-points were abdominal recurrence-free survival (ARFS), distant metastasis-free survival (DMFS) and overall survival (OS). In the STREXIT cohort, the effect of RT administration was explored with a propensity score (PS) matching analysis. The PS was estimated with a multivariable binary logistic model including age, gender, tumor size, tumor grade, multifocality and histological subtype. Patients treated with RT+surgery (RT/S) were matched 1:1 with patients treated with surgery alone (S) according to the PS.

Results: The STRASS and STREXIT cohorts totaled 266 and 831 patients, respectively. Median FU was 43 months (IQR 30-59) in the STRASS cohort and 51mo (IQR 31-67) in the STREXIT cohort. The proportion of patients who were treated with preoperative RT was 50% in STRASS and 16.8% in STREXIT.

Three-year ARFS, DMFS and OS in RT/S patients were 66% (95%CI 57–74%), 68% (95%CI 59–76) and 84% (95%CI 76–89) in STRASS and 71% (95%CI 62–78), 63% (95%CI 54–71) and 79% (95%CI 70–85) in STREXIT (Fig. 1). In patients treated with surgery alone, 3-year ARFS, DMFS and OS were 59% (95%CI 50–67), 68% (95%CI 59–76) and 85% (95%CI 77–90) in STRASS and 61% (95%CI 57–65), 73% (95%CI 69–76) and 82% (95%CI 79–85) in STREXIT (Fig. 1).

The STREXIT 1:1 PS-matched dataset included 262 patients. After PS matching, the HR comparing the risk of RT/S vs S was 0.76 (95%CI 0.51-1.13) for ARFS, 1.30 (95%CI 0.84-2.01) for DMFS and 1.24 (95%CI 0.72-2.13) for OS. In a subgroup analysis of patients with liposarcoma (n=153), the HR comparing the abdominal recurrence risk of RT/S vs S was 0.73 (95%CI 0.42-1.25).

In the unadjusted STREXIT cohort (n=831), the HR comparing ARFS of RT/S vs S was 0.77 (95%CI 0.57-1.04). In a subgroup analysis on patients with liposarcoma (n=544), the HR comparing ARFS of RT/S vs S was 0.69 (95%CI 0.46-1.03). In the pooled STRASS+STREXIT cohort (n=1097), the HR comparing ARFS of RT/S vs S was 0.79 (95%CI 0.63-1.00) in the whole cohort and 0.66 (95%CI 0.48-0.89) in the subgroup of patients with liposarcoma.

In the pooled STRASS+STREXIT 1:1 PS-matched cohort (n=528), the HR comparing the risk of RT/S vs S was 0.80 (95%CI 0.61-1.05) for ARFS, 1.08 (95%CI 0.80-1.45) for DMFS and 1.20 (95%CI 0.82-1.77) for OS.

In the subgroup of patients with liposarcoma, HR comparing ARFS of RT/S vs S was 0.66 (95%CI 0.46-0.94).

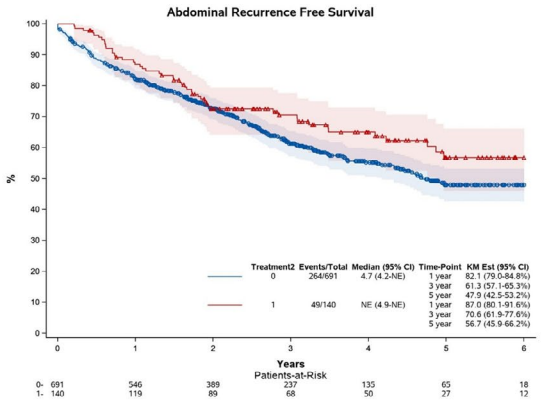
In the cohorts we analyzed, radiotherapy was not associated with any endpoints in subgroup analyses on patients with leiomyosarcoma.

Conclusion: Abdominal recurrence free survival, DMFS and OS of patients with primary RPS treated within or outside STRASS trial were similar.

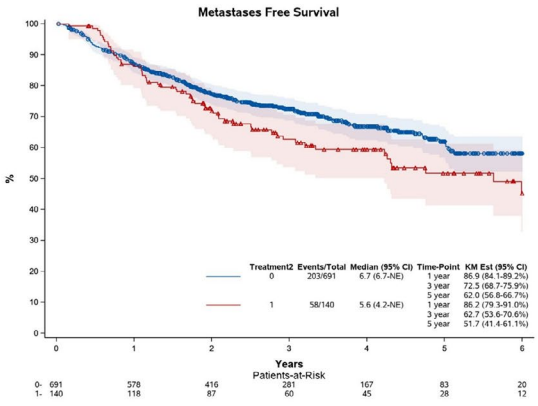
Radiotherapy administration was not associated with OS or DMFS in any of the cohorts we analyzed. The effect of RT on ARFS is intriguing. In the STREXIT 1:1 PS-matched cohort, RT was not associated with ARFS. Pooling together STRASS and the STREXIT 1:1 PS-matched cohort allowed us to increase the power of our analysis. In a subgroup analysis of the STRASS+STREXIT 1:1 PS-matched cohort including only patients with liposarcoma (well-differentiated and dedifferentiated), RT was associated with better ARFS with an HR of 0.66. Similar to STRASS, this study also confirmed that patients with retroperitoneal LMS do not benefit from preoperative radiotherapy.

Figure 1 – STREXIT cohort: abdominal recurrence-free survival (panel A), distant metastasis-free survival (panel B) and overall survival (panel C) after resection of primary retroperitoneal sarcoma in patients treated with surgery alone (blue) or preoperative radiotherapy and surgery (red).

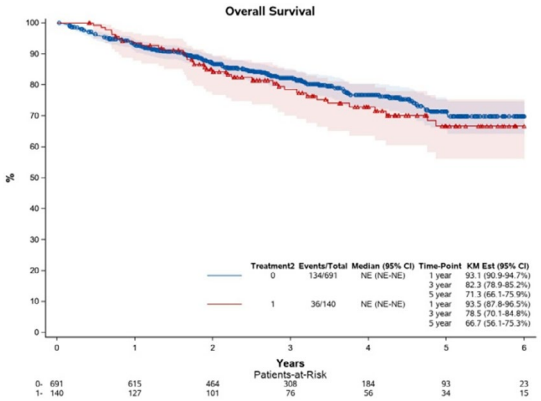
Panel A



Panel B



Panel C



Paper #18 3437448

INTERMUSCULAR MYXOID LIPOSARCOMA CAN BE MANAGED BY MARGINAL SURGICAL RESECTION FOLLOWING NEOADJUVANT RADIOTHERAPY

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Objective: Myxoid liposarcoma (MLS) is a mesenchymal malignancy with adipocyte differentiation accounting for 15-20% of liposarcomas and 5% of adult soft tissue sarcomas. MLS is treated by wide surgical resection in conjunction with radiotherapy and is associated with low rates of local recurrence (LR). Most MLS are located between muscles so wide local excision (WLE) can be quite morbid with adverse functional results and higher complication rates.

MLS are known to be extremely sensitive to radiotherapy which has led to development of protocols utilizing neoadjuvant radiation. Given the radiosensitivity of MLS, we hypothesize that resection of intermuscular MLS with marginal margins (≤1mm) does not result in higher rates of LR or lower overall survival (OS) if performed following neoadjuvant radiotherapy.

Methods: We identified all patients with localized intermuscular MLS who underwent neoadjuvant radiotherapy and surgical resection between 2000-2018 from a prospectively collected database. We calculated the ellipsoid tumour volume (ETV = h x w x d x (π/6)) pre- and post-radiotherapy and determined percent necrosis and margin status following resection based on histological analysis. Demographic and oncologic variables included: age (<50 or ≥50 years), gender, site (upper/lower limb or trunk), tumour grade (1 to 3), necrosis (<90% or ≥90%), tumour size (<10cm or ≥10cm). Response to neoadjuvant radiotherapy was assessed by RECIST criteria based on ETV calculations.

Patients were divided into three groups based on margin status: marginal (≤1mm), WLE (>1mm) and positive (macro- or microscopic). Local recurrence-free and overall survival were calculated using the Kaplan-Meier method and groups were compared using one-way ANOVA or Chi-square/Fisher's exact text, as appropriate. Statistical analysis was conducted using SPSS v26.

Results: Eighty-nine patients met our inclusion criteria, with a mean age of 47 years (range, 17-87) and a male:female ratio of 2.3:1. All patients received neoadjuvant radiotherapy at a dose of 50Gy. Mean patient follow-up was 6.25 years (range, 0.16-16.44). Forty-one patients (46.1%) had marginal margins, while 36 patients (40.4%) had a wide-local excision and the remaining 12 patients (13.5%) had microscopically-positive margins (Table 1).

There was no difference in local recurrence-free survival between marginal and WLE groups (97.4% versus 100% at two years, respectively; p=0.36; Figure 1). Similarly, there was no difference in overall survival between these groups (100% versus 97.2% at two years, respectively; p=0.57; Figure 2). Marginal margins and WLE groups were comparable in all variables studied (Table 2).

Conclusion: There was no difference in local recurrence-free or overall survival for patients with intermuscular MLS who had tumours resected with marginal margins compared with WLE in the setting of neoadjuvant radiotherapy.

Though this is a small single-centre retrospective analysis, it suggests that the standard of WLE is not required to achieve good oncologic outcomes in localized MLS as long as the patients have neoadjuvant radiotherapy.

We are currently expanding this study to include patients from multiple, international sarcoma centres.

Table 1. Breakdown of patients into all Variables & Subgroupings against survival.

Variables	Subgroup	n	%	2-year Overall Survival (%)	Univariate p-value	2-year Disease Free Survival (%)	Univariate p-value
Age at Surgery	<50 years	55	61.8	94.4	0.33	89	0.11
	>50 years	34	38.2	96.9		93.8	
Gender	Male	62	69.7	93.2	0.06	88.2	0.24
	Female	27	30.3	100		96.3	
Site	Upper Limb	5	5.6	80	0.18	80	0.37
	Lower Limb	79	88.8	96.1		90.9	
	Trunk	5	5.6	100		100	
Grade	1	5	5.6	100	0.022	100	0.036
	2	71	79.8	97.1		92.8	
	3	13	14.6	84.6		76.9	
% Necrosis	<90%	34	38.2	100	0.11	90.7	0.52
	>90%	37	41.6	91.7		89	
Size	<10cm	25	28.1	100	0.14	100	0.012
	>10cm	64	71.9	93.6		87.2	
RECIST	1	0	0.0	-	0.0125	-	0.18
	2	64	71.9	96.8		91.9	
	3	23	25.8	95.4		91.1	
	4	2	2.2	50		50	
Margin	Marginal	41	46.1	100	0.058	94.9	0.039
	WLE	36	40.4	97.2		94.3	
	Positive	12	13.5	75		66.7	

Figure 1. Kaplan-Meier analysis of local recurrence based on the type of resection for patients with MLS following neoadjuvant radiation.

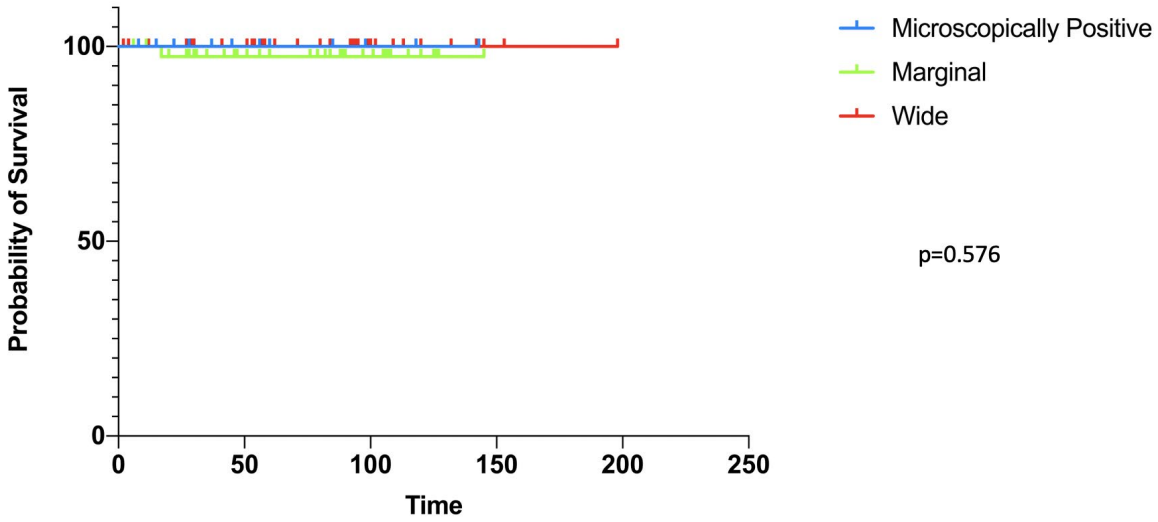
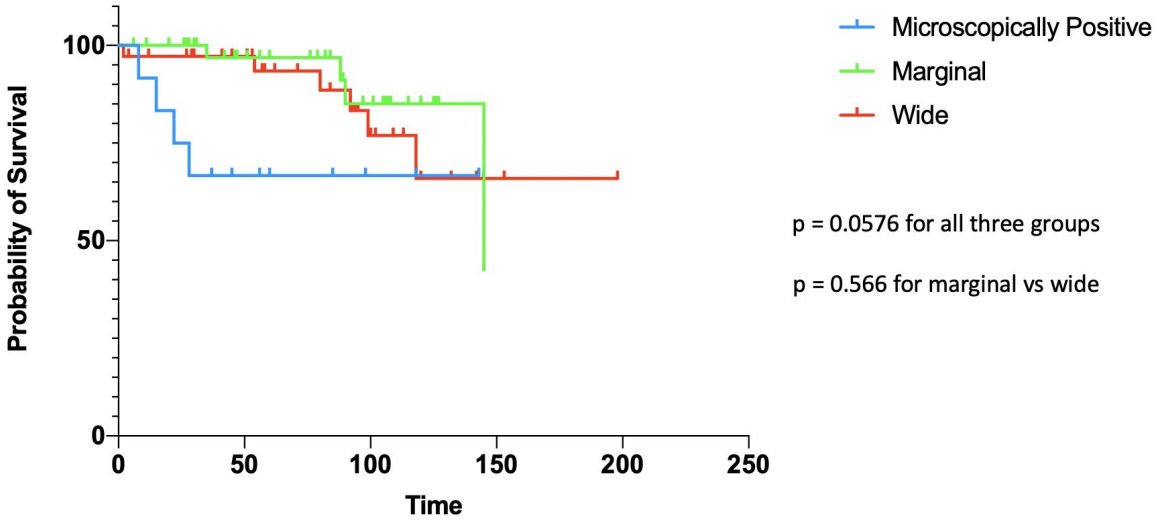


Table 2. Breakdown of patients into Variables & Subgroupings against resection type.

Variable	Subgroup	Marginal		Wide Local Excision		Positive (Microscopically)		p-value (all 3)	p-value (marginal vs WLE)
		n	%	n	%	n	%		
Age at Surgery	<50 years	24	58.5	23	63.9	8	66.7	0.83	0.65
	>50 years	17	41.5	13	36.1	4	33.3		
Gender	Male	29	70.7	26	72.2	7	58.3	0.65	>0.99
	Female	12	29.3	10	27.8	5	41.7		
Site	Upper Limb	0	0.0	3	8.3	2	16.7	0.11	0.077
	Lower Limb	40	97.6	30	83.3	9	75.0		
	Trunk	1	2.4	3	8.3	1	8.3		
Grade	1	1	2.4	1	2.8	3	25.0	0.0093	0.46
	2	36	87.8	29	80.6	6	50.0		
	3	3	7.3	6	16.7	3	25.0		
% Necrosis	<90%	14	34.1	14	38.9	6	50.0	0.94	>0.99
	>90%	12	29.3	12	33.3	4	33.3		
Size	<10cm	9	22.0	12	33.3	4	33.3	0.49	0.311
	>10cm	32	78.0	24	66.7	8	66.7		
RECIST	1	0	0.0	0	0.0	0	0.0	0.023	0.19
	2	34	82.9	25	69.4	5	41.7		
	3	7	17.1	9	25.0	7	58.3		
	4	0	0.0	2	5.6	0	0.0		

Figure 2. Kaplan-Meier analysis of overall survival based on the type of resection for patients with MLS following neoadjuvant radiation.



Paper #19 3437081

DOSE REDUCTION OF PREOPERATIVE RADIOTHERAPY FOR MYXOID LIPOSARCOMA (DOREMY): A PROSPECTIVE, MULTICENTER, SINGLE-ARM, PHASE 2 TRIAL

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Objective: Surgery with conventional preoperative radiotherapy (RT) to 50 Gy in once-daily 2 Gy fractions provides excellent local control in myxoid liposarcomas (MLS). It is, however, associated with morbidity. Particularly wound complications are observed in one third of MLS patients, impacting quality of life and health care costs adversely. In MLS superior volumetric reductions, pathological responses and local control are achieved after preoperative RT, as compared to other subtypes of soft tissue sarcomas. Given this exceptional radiosensitivity of MLS, we aimed to assess whether a dose reduction for this histologic subtype would result in comparable oncological outcome with less morbidity.

Methods: The DOREMY trial (NCT02106312) was designed as a prospective, multicenter, single-arm, phase 2 trial to evaluate the efficacy of a dose reduction of preoperative RT in MLS. The total radiation dose of 36 Gy, was administered in once-daily 2 Gy fractions. The primary endpoint was extensive pathological treatment response in the resected specimen. Treatment effect was assessed during central pathology review by three expert sarcoma pathologists. Secondary endpoints included local control, progression-free survival, disease specific survival, overall survival, wound complications and late toxicity. Wound complications were classified to be minor, moderate, or major, respectively requiring, no or non-invasive intervention without readmission, secondary wound management without secondary operation, or secondary operation. Late toxicity was scored at follow-up visits according to the RTOG late toxicity criteria. Follow-up visits were scheduled three-monthly in year one and two, six-monthly for year three, four and five, and thereafter annually. A Bayesian statistical design was used in order to provide a stopping rule for inefficacy of the reduced dose. The observed pathological response is a binary variable indicating either the presence of ≥50% of histological treatment effects in the treated tumor (success, with probability p) or a histological response of <50% (failure). The trial would have stopped for inefficacy if the posterior probability that p ≥0.7 was <0.05 at any time. The primary outcome, local control, and morbidity data were analyzed per-protocol. Survival endpoints were measured from the date of baseline visit and analyzed by intention-to-treat, using the Kaplan-Meier approach. Univariable analysis by binary logistic regression was performed in order to identify clinical predictive factors for extensive pathological treatment response. The level of significance was p ≤0.05 in all tests.

Results: Between November 2010 and August 2019, 79 patients were enrolled from nine tertiary sarcoma centers in Europe and the US (Table 1). Two patients did not undergo surgery due to development of intercurrent metastatic disease. Extensive pathological treatment response was observed in 70/77 (91%) patients. After a median follow-up of 25 months (IQR 13-38), no local relapses were found. Progression-free survival, disease specific survival and overall survival rates at 3 years were 93%, 96%, and 95%, respectively (Figure 1). An overview of wound complications is presented in Table 2. Late toxicity was classified to be grade 1 in 28/70 (40%), grade 2 in 8/70 (11%), grade 3 in 2/70 (3%), and grade 4-5 in none of the evaluable patients.

Conclusion: The DOREMY trial shows that a dose reduction of preoperative radiotherapy in MLS is effective and oncologically safe. Furthermore, the morbidity of the reduced dose regimen appears to be lower than that of the conventional dose regimen. Less readmissions and reoperations for wound complications, together with decreased treatment time on linear accelerators, are likely to favorably affect patient burden, quality of life and health care costs. As a phase 3 trial is not

feasible in this rare tumor, we propose the new standard radiation dose of preoperative radiotherapy for MLS patients to be 36 Gy in once-daily 2 Gy fractions.

Table 1. Baseline Characteristics

	Total (n=79)	≥ 50% pathological treatment effect (n=70)	< 50% pathological treatment effect (n=7)	p-value
Follow up (months) [IQR]	25 [13-38]	25.2 [13-38]	35 [8-51]	N.S.
Age (years) [IQR]	45 [39-56]	46 [41-55]	43 [40-67]	N.S.
Sex				N.S.
● Female	35 (44%)	30 (43%)	4 (43%)	
● Male	44 (56%)	40 (57%)	3 (57%)	
Presentation				N.A.^
● Primary	77 (98%)	70 (100%)	6 (86%)	
● Recurrence	2 (2%)	0	1 (14%)	
Tumor location				N.S.*
● Proximal lower extremity	62 (78%)	57 (81%)	3 (42%)	
● Distal lower extremity	10 (13%)	8 (11%)	2 (29%)	
● Upper extremity	2 (3%)	1 (1%)	1 (14%)	
● Trunk	5 (6%)	4 (6%)	1 (14%)	
Median tumor diameter (cm) [IQR]	9.9 [7.3-15.9]	10.4 [8.0-16.2]	6.4 [4.3-7.8]	.003
Round Cell Component				N.S.
● 0-5%	61 (77%)	54 (77%)	5 (71%)	
● ≥ 5%	15 (19%)	13 (19%)	2 (29%)	
● Unknown	3 (4%)	3 (4%)	0	
Type of surgery				N.A.^
● Limb sparing or other	76 (96%)	69 (99%)	7 (100%)	
● Amputation	1 (1%)	1 (1%)	0	
● No surgery	2 (3%)	0	0	
Surgical margins				.004
● Negative	72 (94%)	68 (97%)	4 (57%)	
● Positive	5 (6%)	2 (3%)	3 (43%)	

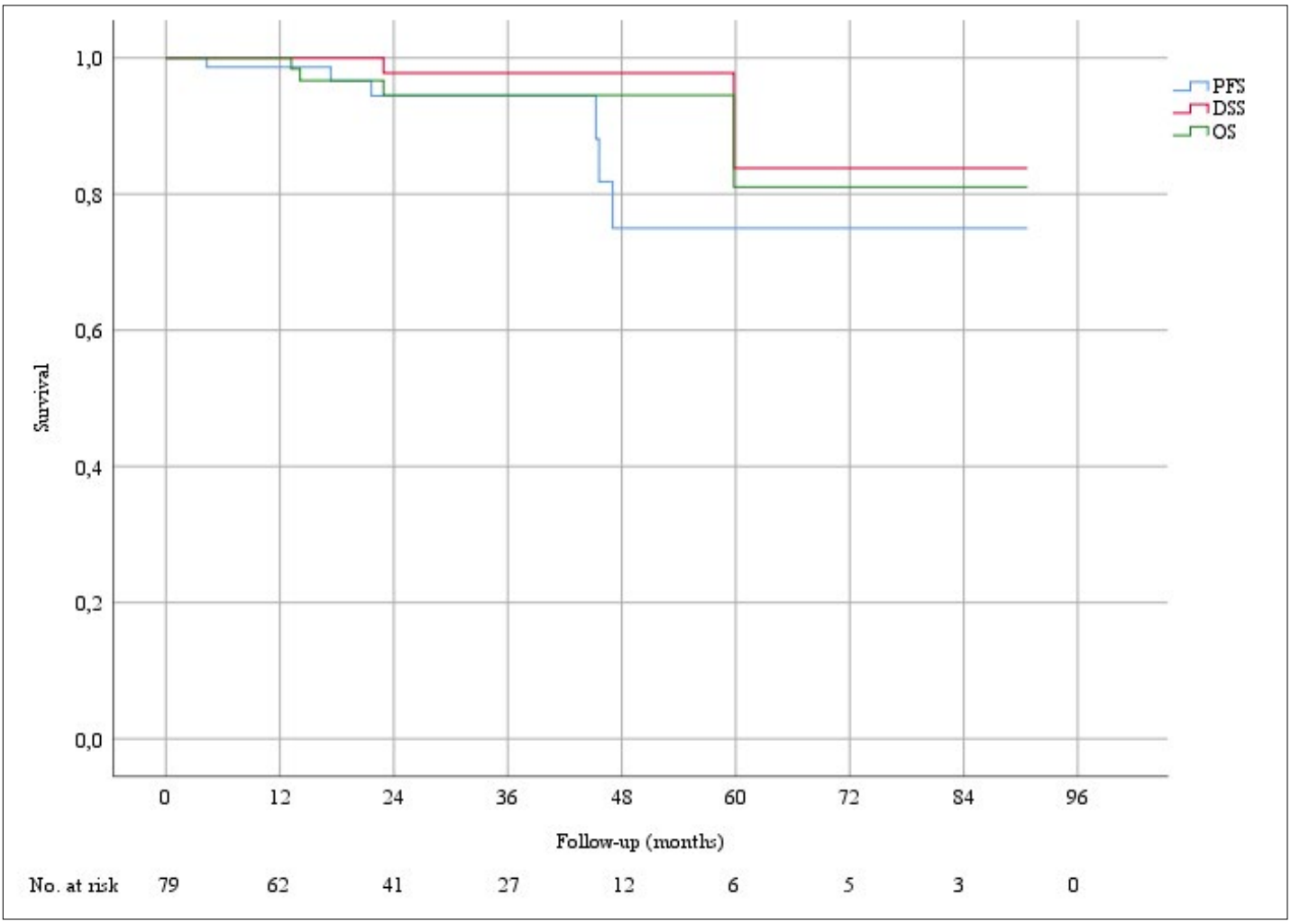
The cumulative values in ≥ 50% and < 50% pathological treatment effect columns do not match the total value since, two patients did not undergo surgery and therefore did not have resection specimens available for analysis.
Abbreviations: IQR= inter quartile range, cm= centimeter, N.S.= not significant, N.A.= not assessed.
Explanation of the symbols: ^No statistic testing was performed, due to small numbers in (at least one of) the subgroups.
*Fisher's exact test of proximal lower extremity vs distal lower extremity.

Table 3. Wound Complication Overview

Wound complication type	Total n (%)	Proximal lower extremity n (%)	Distal lower extremity n (%)	Upper extremity n (%)	Other tumor location n (%)
No wound complication	60 (78%)	48 (80%)	8 (80%)	1 (50%)	3 (60%)
Any wound complication	17 (22%)	12 (20%)	2 (20%)	1 (50%)	2 (40%)
Minor wound complication	4 (5%)	1 (2%)	1 (10%)	1 (50%)	1 (20%)
Moderate wound complication	8 (10%)	7 (12%)	1 (10%)	0	0
Major wound complication	5 (6%)	4 (7%)	0	0	1 (20%)
Wound complication necessitating any intervention (moderate/major)	13 (17%)	11 (18%)	1 (10%)	0	1 (20%)
Total surgery cases	77 (100%)	60 (78%)	10 (13%)	2 (3%)	5 (7%)

Wound complication data available for all 77 patients, stratified by tumor location.

Figure 1. Kaplan-Meier survival curves for progression free survival (PFS), disease specific survival (DSS), and overall survival (OS).



Paper #20 3461475

A PHASE 2/3, RANDOMIZED, DOUBLE BLIND, CROSS-OVER, STUDY OF SELINEXOR VERSUS PLACEBO IN ADVANCED UNRESECTABLE DEDIFFERENTIATED LIPOSARCOMA (DDLS)

Mrinal Gounder[1], *Albiruni Abdul Razak*[2], *Neeta Somaiah*[3], *Javier Martin-Broto*[4], *Scott Schuetze*[5], *Giovanni Grignani*[6], *Sant P. Chawla*[7], *Bartosz Chmielowski*[8], *Bruno Vincenzi*[9], *Silvia Stacchiotti*[10], *Andrew J. Wagner*[11], *Axel Le Cesne*[12], *Richard F. Riedel*[13], *Robin L. Jones*[14], *Kristen Ganjoo*[15], *Xavier Garcia del Muro*[16], *Melissa A. Burgess*[17], *Dayana Michel*[18], *Hongwei Wang*[18], *Jatin J. Shah*[18], *Steven Attia*[19]

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Objective: DDLS is an aggressive sarcoma with a metastatic rate of 10%–20% and overall mortality of 50%–75%. Surgery is the cornerstone of the management of resectable DDLS. However, unresectable or metastatic DDLS has limited systemic options and the overall survival is 9 – 20 months. The current approved drugs for DDLS are comprised of only cytotoxic-chemotherapeutic drugs. There is a significant unmet medical need for new drugs for advanced DDLS.

Selinexor is an oral, selective inhibitor of nuclear export that specifically inhibit exportin 1 (XPO1), leading to the nuclear accumulation and reactivation of tumor suppressor proteins. Selinexor with low dose dexamethasone was approved for the treatment of patients with triple-class refractory multiple myeloma and selinexor monotherapy was also recently approved for patients with relapsed and refractory diffuse large B cell lymphoma. Selinexor demonstrated anti-tumor activity against DDLS in preclinical studies and in a phase 1b trial in patients with soft tissue sarcomas. Based on these data, we initiated a phase 2/3 study of selinexor in advanced DDLS post first line systemic therapy.

In the phase 2 portion, based on RECIST 1.1 the mPFS was 5.5 months for selinexor compared with 2.7 months (placebo), (landmark analysis, p=0.10). Common adverse events were mostly grade 1/2 and included nausea, fatigue, anorexia and weight loss. These promising data resulted in continuation to the phase 3 portion of the study, with a modification to include patients with DDLS who had received at least 2 and no more than 5 prior lines of systemic therapy as well as a change of response evaluation criteria from WHO to RECIST. Selinexor may represent an oral non-chemotherapy treatment option for patients with non-resectable and metastatic DDLS.

Methods: This is a phase 2/3 multicenter, randomized, double-blind, placebo-controlled study in patients with relapsed DDLS. In the phase 3 portion of the study, patients aged ≥12 years, with histologic confirmation of DDLS, with radiologic evidence of progressive disease within 6 months prior to randomization, and who have had at least 2 but no more than 5 prior systemic therapies are eligible for enrollment. Approximately 277 eligible patients will be randomized 2:1 to receive oral selinexor 60 mg twice weekly or placebo. Randomization is stratified based on prior eribulin and trabectedin use, and the number of prior systemic therapies (2 versus ≥ 3). Treatment assignment can be unblinded for patients with central confirmation of disease progression. Patients who were initially assigned to placebo arm may crossover to receive open-label selinexor and patients on the selinexor arm may continue to receive selinexor if deriving clinical benefit per investigator's discretion. The revised primary endpoint is PFS by RECIST 1.1 assessed centrally by Independent Centralized Review. Key secondary endpoints include overall survival for non-inferiority/superiority, time to progression, and assessment of safety.

Results: In this ongoing phase 3 study, 267 patients have been enrolled at 61 sites globally at the time of the abstract submission. As of 1 June 2020 data cut, of the first 256 patients whose data was available in database, median age was 65 (range 36 - 85), 161 (63%) were male, 77% were white, 16% other, and 4% Asian, and 45% reside in the USA, 13% in Italy, 13% in France, and 12% in Spain.

Conclusion: Selinexor is a first in class oral XPO1 inhibitor approved in multiple myeloma and diffuse large B cell lymphoma. This is the first global phase 3 trial exclusively in patients with, and the largest study to date in patients with advanced DDLS. Final data analysis for the primary PFS endpoint and preliminary analysis for the secondary endpoints are expected to be available for presentation at CTOS 2020.

Paper #21 3447775

NEUTROPHIL-TO-LYMPHOCYTE RATIO IS A PROGNOSTIC FACTOR REGARDLESS PREOPERATIVE TREATMENTS IN PRIMARY RETROPERITONEAL SARCOMA

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Objective: Outcome prediction in retroperitoneal sarcoma (RPS) is based upon patient age, tumor-related and treatment-related variables. Presently no accurate prognostic biomarkers are available. Neutrophil-to-lymphocyte ratio (NLR) and Platelets-to-lymphocyte ratio (PLR), hemoglobin (Hb) and albumin (Alb) have been associated to prognosis in several solid tumors. Data on these biomarkers in sarcomas are overall limited, and completely lack for RPS. We aimed to investigate the prognostic role of NLR, PLR, Hb and Alb in a large mono-institutional series of RPS.

Methods: A retrospective observational study analysed consecutive primary RPS operated at a single center (2002-2016). Prognostic impact of baseline NLR, PLR, Hb and Alb was studied on overall survival (OS) as primary endopoint. Secondary aims: the prognostic role of NLR changes after preoperative treatments and the correlation between these biomarkers and postoperative morbidity (Clavien-Dindo grade ≥3). Patient and tumor variables were extracted from a prospective institutional database. Baseline NLR, PLR, Hb and Alb were retrospectively retrieved from patients' files. Data base lock for follow-up update was on June 15th 2019.

Correlation between NRL, clinico-pathologic variables and morbidity was studied by Kruskal-Wallis test. OS was analyzed by Kaplan-Meier. The prognostic effect of biomarkers was adjusted for age, malignancy grade and histology subtype at multivariate Cox model. Correlation between pre- and post-treatment values, association of changes with type of treatment were studied by univariate ANOVA and logistic regression, as appropriate.

Results: In the study period 463 patients underwent surgery for primary RPS. Median follow-up was 57 months, with 142 events for OS; 57 (12.3%) patients received preoperative chemotherapy, 51 (11.0%) chemoradiation, and 41 (8.9%) radiation-therapy; before treatment NLR and PLR values were available in 422 (91.1%) patients, Hb in 445 (96.1%), and Alb in 210 (45.4%). Frequency distribution of baseline values is represented in Figure 1. High NLR and PLR, as well as low Hb and Alb were associated with poor OS at univariate analysis (Figure 2). At multivariate analysis excluding Alb, NLR was the only biomarker independently associated to OS, with an hazard ratio of 1.05 (95%CI, 1.01-1.09, p=.01) when adjusted for existing prognostic factors, meaning a 5% increase of the risk of death for each unit increase of NLR (Table 1). An exploratory multivariate analysis which was conducted in the subgroup of patients with known Alb (N=210) confirmed NLR as the only prognostic biomarker. In 149 patients receiving preoperative therapies, NLR changes after treatment did not correlate with the type of delivered treatment (Figure 3) nor with OS. Serious postoperative morbidity was not significantly associated to the considered baseline biomarkers.

Conclusion: NLR seems to have a prognostic value also in primary RPS. If prospectively and externally validated, this may well be included within available prognostic tools. Actually NLR may indirectly reflect tumor/host relationship, the understanding of which is critical to develop immune-modulated strategies. Further studies are needed to investigate the effect of NLR in each single RPS histologic subtype, and the association between NLR and intratumoral infiltrate. Baseline NLR is a readily available biomarker independently associated to survival also in patients affected by primary RPS. Changes of NLR after preoperative treatment is not associated with prognosis and preoperative NLR values do not predict post-operative morbidity.

Table

Variable	Wald Test	p value	Hazard Ratio	95% CI
Age	12.4	<.0001	1.03	1.01 - 1.04
FNCLCC Grade				
G1	57.7	<.0001		
G2	11.1	.001	3.16	1.61 - 6.22
G3	43.8	<.0001	8.89	4.66 - 16.98
NLR	6.6	.01	1.05	1.01 - 1.09

Figure 1.

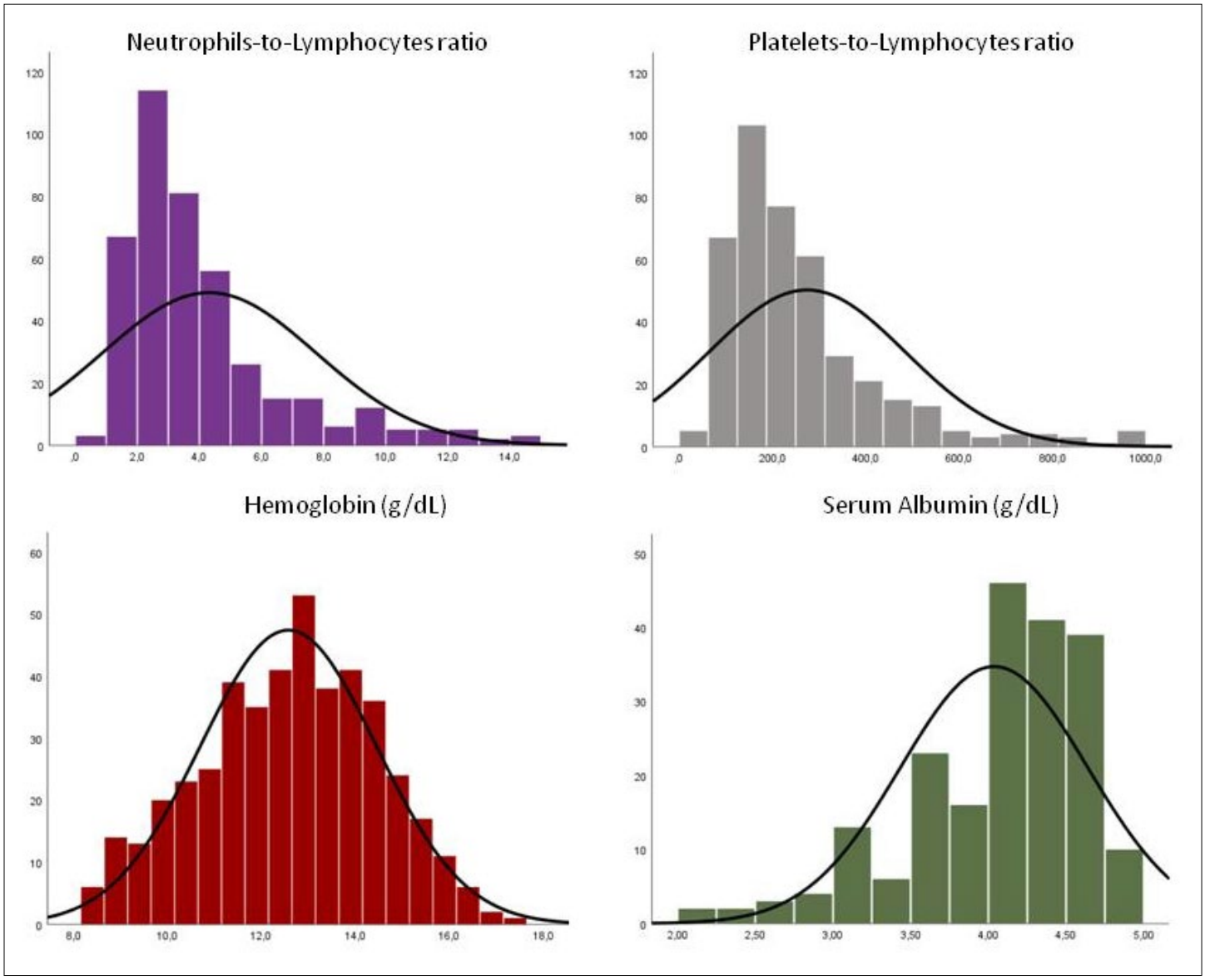


Figure 2.

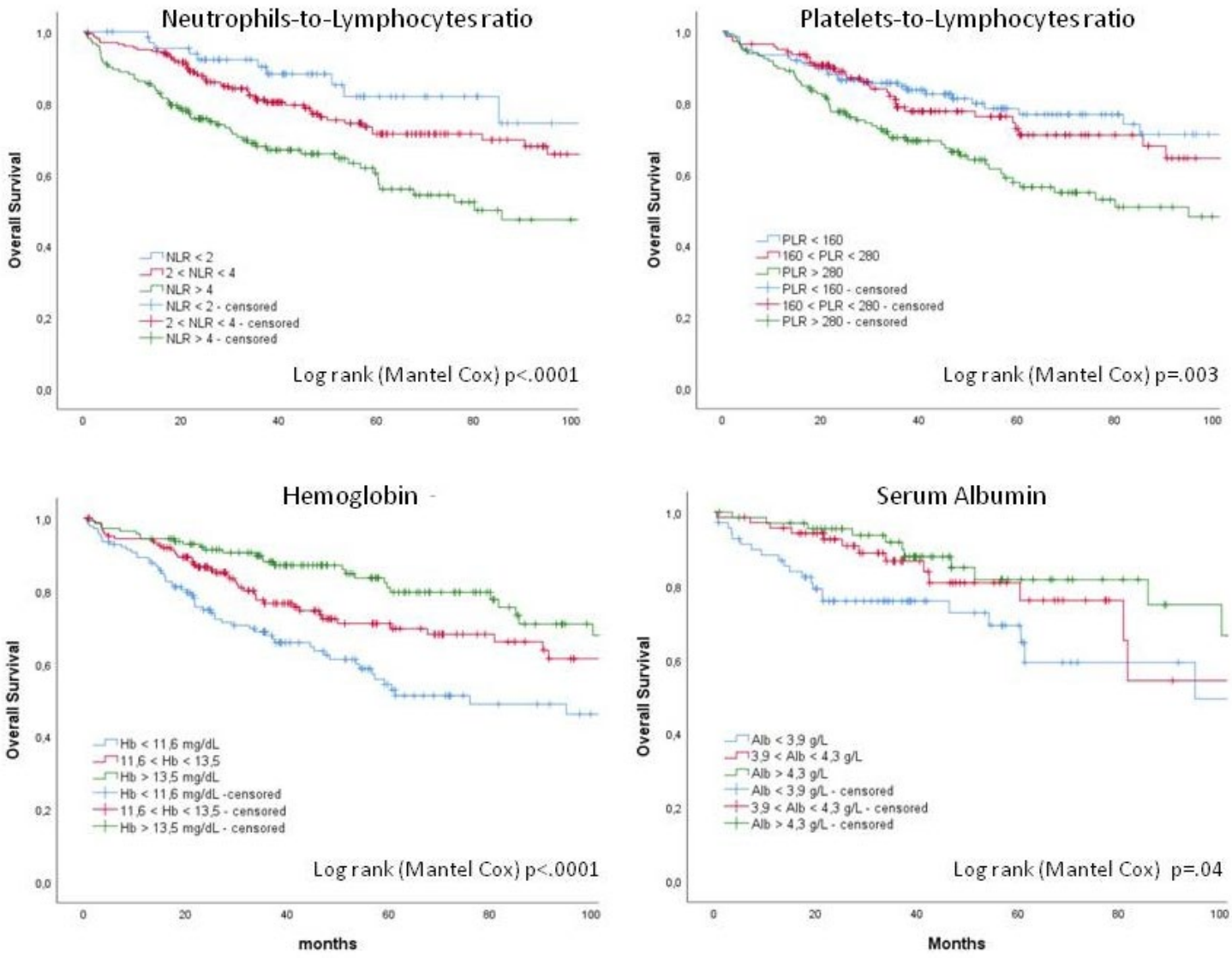
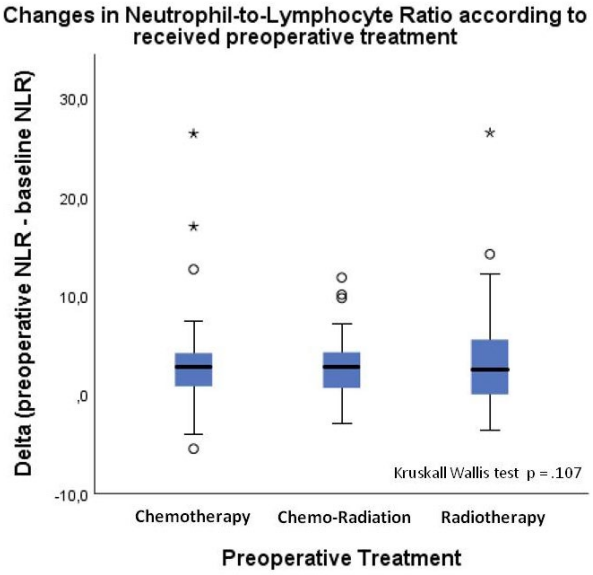


Figure 3.



11:30 am - 12:30 pm

– Session 8 –

GIST

Paper #22 3462544

HUMAN SUCCINATE DEHYDROGENASE-DEFICIENT GASTROINTESTINAL STROMAL TUMORS ARE SENSITIVE TO TEMOZOLOMIDE VIA INDUCTION OF ER STRESS AND DNA DAMAGE

Mayra Yebra[1], Avi Kumar[2], Adam Burgoyne[3], Chih-Min Tang[1], Hyunho Yoon[1], Sudeep Banerjee[4], Joseph Aguilera[1], Thekla Cordes[1], Vipul Sheth[5], Sangkyu Noh[1], Rowan Ustoy[1], Sunil Advani[1], Christopher Corless[7], Michael Heinrich[6], Razelle Kurzrock[1], Scott M. Lippman[1], Paul T. Fanta[1], Olivier Harismendy[1], Christian Metallo[1], ***Jason K. Sicklick***[1]

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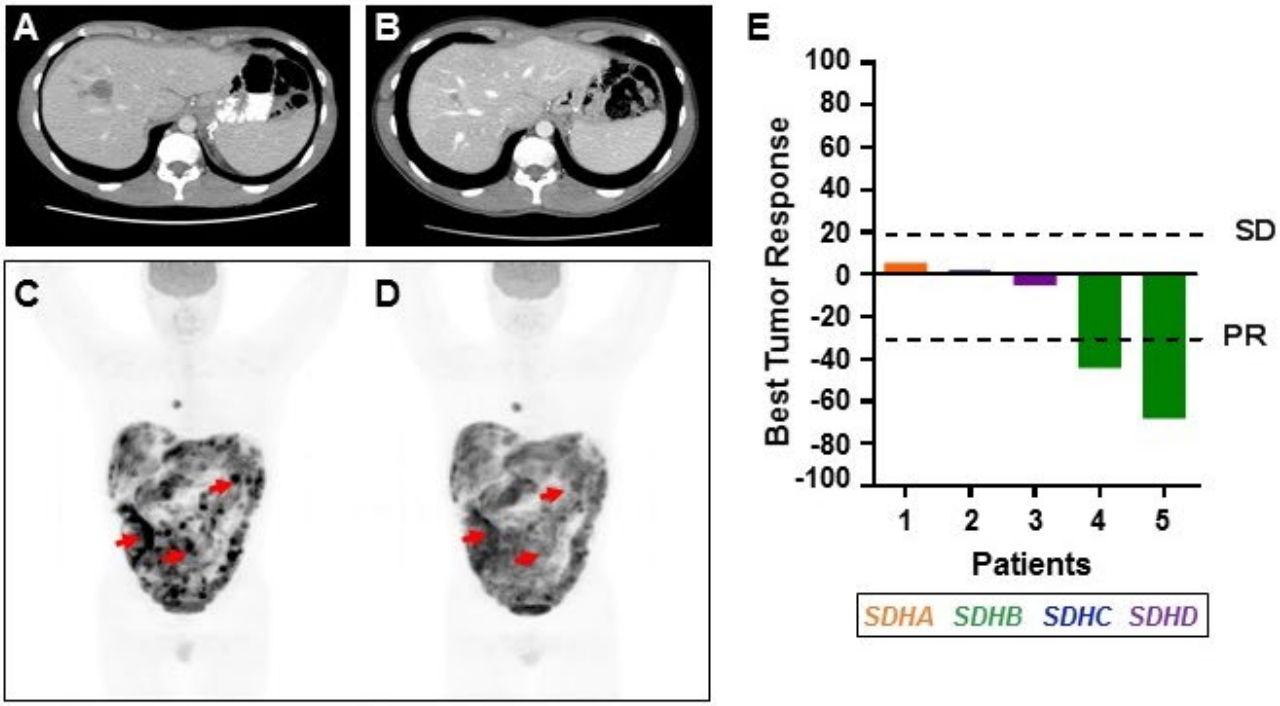
Objective: Gastrointestinal stromal tumors (GIST) harboring *KIT* or *PDGFRA* mutations are sensitive to tyrosine kinase inhibitors (TKIs). In contrast, hereditary GISTs caused by mutations in the succinate dehydrogenase (SDH) enzyme complex are often TKI resistant and a lack of human models for these *SDH*-mutant GIST has limited discovery of novel therapies for this subgroup.

Methods: Primary GIST cells were isolated from resected human *SDH*-mutant GISTs and expanded on a laminin-rich extracellular matrix (2D). These cells were propagated in 2D cultures and as 3-dimensional (3D) spheroids. Colony formation was assessed in soft agar and 1% methylcellulose. Immunofluorescence staining was used to detect expression of the GIST markers, KIT and DOG-1. SDHB proteins levels were assessed by both immunoblotting and immunofluorescent staining. RNA sequencing analysis of these cultures and their parental tumors was performed to compare their molecular profiles. Targeted metabolomic analysis and Seahorse assays were performed to examine metabolic alterations. Sensitivity to temozolomide (TMZ) was assessed by CellTiterGlo, γ-H2AX immunostaining, the neutral comet assay, and immunoblotting for markers of ER stress and apoptosis. We have subsequently treated SDH-deficient GIST patients with TMZ.

Results: We have developed three patient-derived SDH-deficient GIST cell cultures that express GIST markers, KIT and DOG-1, can be expanded on a matrix, and form colonies in soft agar and methylcellulose. In addition, they have molecular profiles similar to their parental tumors. Moreover, they possess metabolic hallmarks of SDH deficiency (i.e. very low to undetectable SDHB protein levels, induction of hypoxia-regulated genes, and accumulation of succinate). Importantly, treatment of these cells with TMZ induced DNA damage, expression of the ER stress markers, C/-EBP homologous protein (CHOP) and glucose-regulated protein 78 (GRP78/BiP), as well as p21 (WAF1/Cip1), a cell cycle arrest marker, and death receptor 5 (DR5), a transcriptional target of CHOP. Additionally, TMZ treatment resulted in Bax activation and cell death. Finally, we assessed the treatment efficacy of TMZ in a cohort of 5 SDH-deficient GIST patients and found a 40% objective response rate and 100% disease control rate, suggesting this could be a promising treatment for these patients.

Conclusion: Here we report the generation and characterization of patient-derived SDH-deficient GIST cell cultures that recapitulate the cellular, metabolic, and molecular biology, as well as TKI-resistance of parental tumors. These models were interrogated to identify temozolomide as an inducer of toxicity *in vitro* and led to the discovery that temozolomide is a promising therapy for SDH-deficient GIST patients. A phase II trial is currently underway and being expanded to additional sites.


A
B
C
D
E
Best Tumor Response
100
80
60
40
20
0
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-40
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SD
PR
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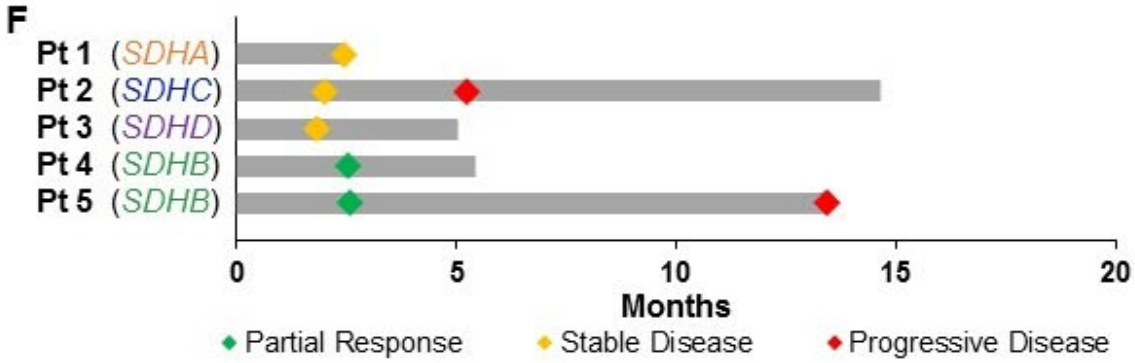
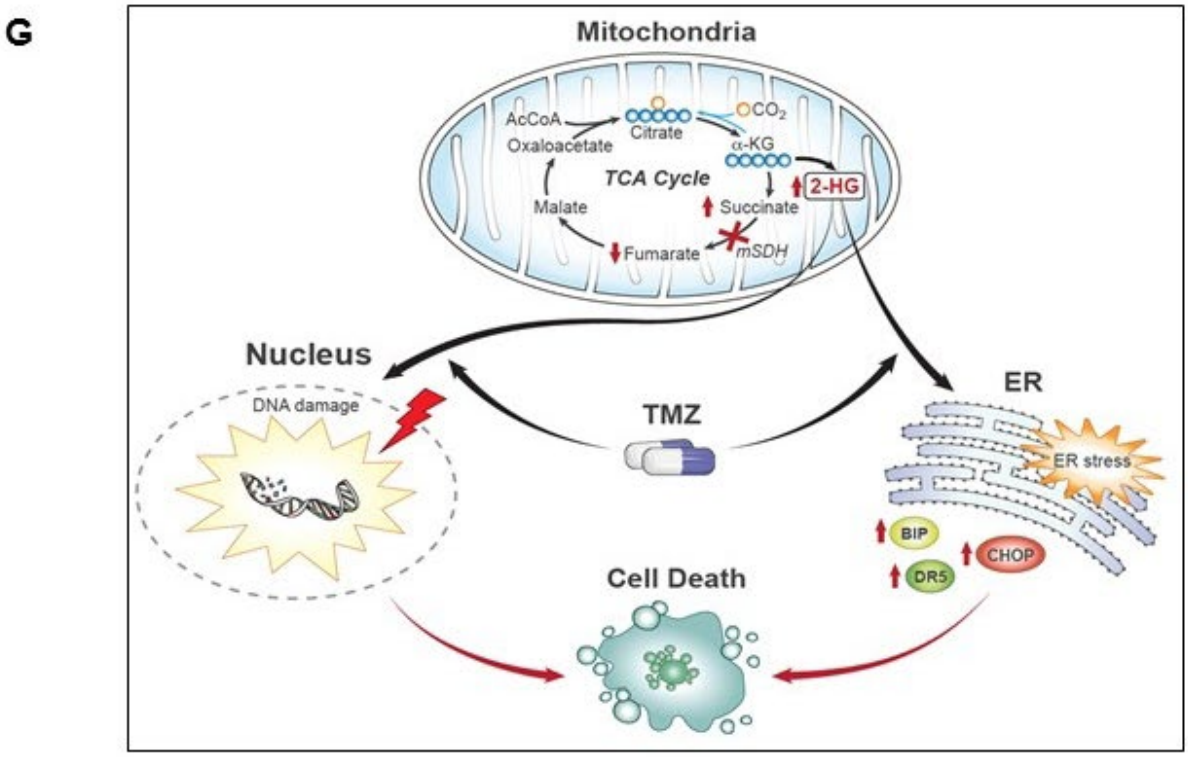
4
5
Patients
SDHA SDHB SDHC SDHD


F
Pt 1 (SDHA)
Pt 2 (SDHC)
Pt 3 (SDHD)
Pt 4 (SDHB)
Pt 5 (SDHB)
0
5
10
15
20
Months
Partial Response
Stable Disease
Progressive Disease


G
Mitochondria
AcCoA
Oxaloacetate
Citrate
CO2
α-KG
TCA Cycle
2-HG
Malate
Succinate
Fumarate
mSDH
Nucleus
DNA damage
TMZ
ER
ER stress
BIP
CHOP
DR5
Cell Death

Paper #23 3465722

ASSESSMENT OF A GUIDELINE-BASED FOLLOW-UP STRATEGY AFTER COMPLETE SURGERY IN PATIENTS AFFECTED BY GASTROINTESTINAL STROMAL TUMOR (GIST) WITH LOW-RISK OF RECURRENCE

Lorenzo D'Ambrosio[1], *Elena Fumagalli*[2], *Margherita Nannini*[3], *Tommaso Martino De Pas*[4], *Bruno Vincenzi*[5], *Francesca Ligorio*[2], *Elisabetta Pennacchioli*[6], *Andrea Mogavero*[1], *Antonella Brunello*[7], *Fabio Conforti*[4], *Danila Comandini*[8], *Giulia Manessi*[1], *Silvia Gasperoni*[9], *Virginia Ferraresi*[10], *Giuseppe Badalamenti*[11], *Sandra Aliberti*[1], *Marco Fiore*[12], *Maria Pantaleo*[3], *Giovanni Grignani*[1]

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Objective: GIST follow-up is recommended by both ESMO and NCCN guidelines primarily aiming to anticipate detection of recurrences in order to optimize further treatment and eventually improve patients' outcome. Despite not proven, the benefit of an earlier relapse/progression recognition needs to be weighed against both costs (economic plus biologic related to x-rays exposure) and potential anxiety generated by medicalization (*e.g.:* test result anxiety). Of course, this non-trivial trade-off is highly affected by the widely spread relapse-risk of GISTs. In this project, we assessed the performance of a regular follow-up to detect recurrence and other clinically relevant events (i.e. second tumors) in GIST patients entailing a very-low to low risk of relapse.

Methods: This was a retrospective observational study based on series of patients treated within Italian Sarcoma Group (ISG) reference centers. We included patients affected by surgically removed and histologically proven GIST not treated with adjuvant imatinib because of a low-risk of relapse (according to the Armed Forces Institute of Pathology criteria). Patients had to have a follow-up according to ESMO guidelines. We calculated the number of tests identifying a relapse/tumor on the total CT performed, the number of relapses detected with non-imaging procedure (e.g.: EGDS), the average size of relapse. Disease-free survival (DFS), overall survival (OS), GIST-specific survival (GIST-SS), and second-tumor specific survival (ST-SS) were estimated according to Kaplan and Meier method and comparisons between groups made with the log rank test and hazard ratio estimates with their 95% confidence intervals. Univariable and multivariable Cox regression models were used to identify variables associated with recurrence, second tumor and overall mortality. Multivariable Cox regression model for each outcome included all predictors that were significant in the univariable analysis for that outcome. All tests were two-sided with significance level set at 0.05. Analyses were performed using SPSS v26.0. The study protocol was approved by the IRB of Candiolo Cancer Institute.

Results: A total of 554 patients were included in the final analyses. Patients characteristics are described in Table 1. Median follow up for the whole population was 63 months with an estimated OS, DFS and GIST-SS at 10 and 20 years of 91% and 77%, 91% and 73%, 96% and 90%, respectively. We observed 37 (6.8%) recurrences detected by CT scan (30), or endoscopy (4), or abdominal ultrasound (3) involving primary and distant sites in 9 (1.6%) and 28 (5.1%) cases, respectively. Recurrences occurred in 8/37 (21%) patients after 10 years or more. Non-gastric primary and presence of symptoms at diagnosis were associated with a higher risk of relapse (HR 2.57, 95%CI 1.33-4.95, p=0.005; HR 2.15, 95%CI 1.04-4.48, p=0.040; respectively). According to ESMO guidelines, 4930 abdominal CT scans were to be performed in a 10-year FU for the whole series. This translates in 133 CTs to be performed to detect one recurrence. Finally, second tumors were diagnosed in 43 (7.8%) patients during FU.

Conclusion: In this large series of GIST patients selected for having a low risk of relapse, the latter was spread over 10 years and more. In a subset of patients with a nearly long-term 10% risk of dying of their GIST, these data highlight the need of an open and thoroughly shared decision-making regarding the FU intensity between patients and their physicians taking into account costs (ionizing radiation exposure, medicalization and economic burden) and benefit (earlier recurrence detection). In this specific setting, how to reshape active surveillance remains challenging.

Table 1. Patient demographic and baseline characteristics

Patients eligible for analyses, n (%)	**554 (100)**
Age at diagnosis (years)	.
Median (range)	62 (18-86)
<65 year-old	321 (57.9)
≥65 year old	233 (42.1)
Gender, n (%)	.
Male	292 (52.7)
Female	262 (47.3)
Tumor site, n(%)	.
Stomach	379 (68.4)
Duodenum	51 (9.2)
Small bowel	103 (18.6)
Large bowel/rectum	13 (2.3)
Other	8 (1.4)
Tumor size, n (%)	.
≤5 cm	432 (78.0)
>5 & <10 cm	110 (19.9)
Not reported	12 (2.2)
Mitotic count (per 50 HPF), n (%)	.
≤5	516 (93.1)
>5 & <10	14 (2.5)
Not reported	24 (4.3)
Symptoms at diagnosis, n (%)	.
No	285 (51.4)
Yes	203 (36.6)
Not reported	66 (11.9)
Bleeding at diagnosis, n (%)	.
No	312 (56.3)
Yes	120 (21.7)
Not reported	122 (22.0)
Type of surgery, n (%)	.
Laparoscopic	132 (23.8)
Laparotomic	305 (55.1)
Endoscopic	46 (8.3)
Radicality of surgery, n (%)	.
R0	438 (79.1)
R1	30 (5.4)
Second tumors, n (%)	.
Overall	158 (28.5%)
Before GIST	70 (12.6%)
Synchronous with GIST	45 (8.1%)
After GIST	43 (7.8%)

HPF, high-power field.

Paper #24 3458521

THE POTENT AND SELECTIVE KIT INHIBITOR PLX9486 DOSED IN COMBINATION WITH SUNITINIB DEMONSTRATES PROMISING PROGRESSION FREE SURVIVAL (PFS) IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR (GIST): FINAL RESULTS OF A PHASE 1/2 STUDY

Jonathan Trent[1], *William D. Tap*[2], *Rashmi Chugh*[3], *Gabriel Tinoco*[4], *Athanasios Tsiatis*[5], *Paul Severson*[5], *Kerry Inokuchi*[5], *Chao Zhang*[5], *Glenn Michelson*[7], *Andrew J. Wagner*[6]

[1]University of Miami, Miami, Florida, UNITED STATES; [2]Memorial Sloan Kettering Cancer Center, New York, New York, UNITED STATES; [3]University of Michigan, Ann Arbor, Michigan, UNITED STATES; [4]The Ohio State University, Columbus, Ohio, UNITED STATES; [5]Plexxikon, Inc., Berkeley, California, UNITED STATES; [6]Dana-Farber Cancer Institute, Boston, Massachusetts, UNITED STATES; [7]KIQ Bio, San Francisco, California, UNITED STATES

Objective: Most metastatic GISTs have primary mutations in KIT exon 9 or 11, which confer sensitivity to imatinib and other tyrosine kinase inhibitors (TKI). Clonal secondary mutations, typically in exons 13, 14, 17, and 18, often confer resistance to initial therapy. PLX9486 is a type I KIT inhibitor that inhibits primary KIT mutations and exon 17 and 18 secondary mutations. Sunitinib is a type II inhibitor which inhibits KIT primary mutations and exon 13 and 14 secondary mutations. A combination of PLX9486 with sunitinib may have activity against a broader spectrum of KIT mutations by blocking both active and inactive conformations.

Methods: 3 + 3 dose escalation study in patients with GIST who had progressed on imatinib. Safety, efficacy per RECIST 1.1, and pharmacokinetics were assessed. The clinical benefit rate (CBR, CR + PR + SD≥16 weeks) and Progression Free Survival (PFS) were assessed. Circulating tumor (ct) DNA was assessed as a biomarker. Three combination dose levels were studied: dose level 1, PLX9486 500mg + sunitinib 25mg; dose level 2, PLX9486 1000mg + sunitinib 25mg; and dose level 3, PLX9486 1000mg + sunitinib 37.5mg. Study drugs were administered orally, once daily.

Results: A total of 18 previously treated GIST patients were enrolled into the combination of PLX9486 and sunitinib, including 3 who crossed over from the single agent PLX9486 group or PLX9486 + PLX3397 (a CSF1R inhibitor) group. Three patients were enrolled in dose level 1, 5 in dose level 2, and 10 in dose level 3. Nine patients were male, median age was 62 years (range 44-78), all patients had received prior imatinib, and the median number of prior TKIs was 4 (range 1-6) and 12/18 had at least 3 prior lines of therapy. The most common grade 3 or 4 treatment-emergent AEs in ≥2 patients were anemia (n=4), hypophosphatemia, diarrhea, and lymphopenia (n=2 each). Importantly, there were no dose limiting toxicities in the 3 dose levels studied. The most common reason for study drug discontinuation was disease progression. CBR was 80% including 1 CR and 2PRs recorded as best responses. The median PFS was 12 months in the 15 PLX9486-naive patients, with 4 patients remaining on study as of the time of the data cut-off (1 CR, 2PR, and 1 SD). Co-administration of sunitinib increased the exposure of PLX9486 whereas exposure of sunitinib was within the expected range. Analysis of ctDNA showed reductions in variant allele frequency compared to baseline for a broad spectrum of KIT mutations including activation loop (exon 17 & 18) mutations which are resistant to sunitinib, demonstrating anti-tumor activity.

Conclusion: Combined inhibition of KIT mutations in GIST is feasible and tolerable with PLX9486 and sunitinib. The Recommended Phase 2 Dose of the combination is 1000mg of PLX9486 and 37.5mg of sunitinib orally once daily. The combination was active in patients with heavily pretreated GIST (majority of patients ≥3rd line) with the majority of patients experiencing clinical benefit with a median PFS of 12 months in the PLX9486 naïve group, and 11 months for the entire group of 18 patients.The mature median PFS compares favorably to single agent sunitinib and other TKIs used in 2nd or later lines of therapy with a safety profile similar to single agent sunitinib. The trial data validates the hypothesis that co-targeting the active and inactive conformations of KIT can provide substantial clinical benefit over type I or type II inhibitors alone, and supports the further exploration of the combination in pre-treated GIST.

Paper #25 3463167

RIPRETINIB INTRA-PATIENT DOSE ESCALATION FOLLOWING DISEASE PROGRESSION PROVIDES CLINICALLY MEANINGFUL PROGRESSION-FREE SURVIVAL IN GASTROINTESTINAL STROMAL TUMOR IN PHASE 1 STUDY

Suzanne George[1], *Ping Chi*[2], *Michael Heinrich*[3], *Margaret von Mehren*[4], *Robin L. Jones*[5], *Kristen Ganjoo*[6], *Jonathan Trent*[7], *Hans Gelderblom*[8], *Albiruni Abdul Razak*[9], *Michael Gordon*[10], *Neeta Somaiah*[11], *Julia Jennings*[12], *Kelvin Shi*[12], *Rodrigo Ruiz-Soto*[12], *Filip Janku*[13]

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Objective: Ripretinib is an FDA-approved switch-control tyrosine kinase inhibitor (TKI) that broadly inhibits mutant KIT and PDGFRA kinase signaling. In the phase 3 INVICTUS study (NCT03353753), ripretinib significantly improved progression-free survival (PFS) vs placebo in patients (pts) with ≥4th-line gastrointestinal stromal tumor (GIST). Here, we report the phase 1 study (NCT02571036) intra-patient dose escalation (IPDE) experience in GIST patients across multiple lines of therapy.

Methods: In this dose-escalation and expansion phase 1 study, patients with 2nd, 3rd, and ≥4th-line GIST were treated with ripretinib 150 mg QD. Investigator-assessed RECIST response assessments were performed every 2 cycles and patients with progressive disease (PD) could dose escalate to ripretinib 150 mg twice a day (BID). PFS period 1 (PFS1; 150 mg QD) was calculated from Cycle 1, Day 1 to PD; PFS2 (150 mg BID) from date of IPDE to 2nd PD or death. Treatment-emergent adverse events (TEAEs) were summarized by PFS1 and PFS2 onset periods and compared descriptively.

Results: In the phase 1 study, 142 GIST patients (2nd line, n=31; 3rd line, n=28; and ≥4th line, n=83) were enrolled in dose-escalation and expansion phases and received at least 1 dose of ripretinib 150 mg QD. In all lines, patients received additional benefit from ripretinib 150 mg BID (**Table**); data as of Aug 31, 2019. TEAEs reported by the 64 patients in PFS1 and PFS2 periods were similar; the most common TEAEs (≥10%) were alopecia, myalgia, nausea, fatigue, palmar-plantar erythrodysesthesia syndrome, muscle spasms, rash, weight decreased, abdominal pain, diarrhea, back pain, vomiting and decreased appetite. In PFS2, anemia and dyspnea were also reported in ≥10% of patients.

Conclusion: Ripretinib dose escalation to 150 mg BID after PD showed an additional PFS clinical benefit across all treatment lines with a similar safety profile compared to that observed with a 150 mg QD dosing regimen. The phase 3 INTRIGUE study (NCT03673501), a randomized, multicenter, open-label study, is investigating ripretinib in the 2nd line vs sunitinib in patients with advanced GIST after treatment with imatinib.

Table

	Ripretinib 150 mg QD (n=142)			Ripretinib 150 mg BID (n=64)		
Line of Therapy	2nd Line (n=31)	3rd Line (n=28)	≥4th Line (n=83)	2nd Line (n=8)	3rd Line (n=17)	≥4th Line (n=39)
mPFS	10.7 months	8.3 months	5.5 months	PFS1, 8.3 months PFS2, 5.6 months	PFS1, 8.3 months PFS2, 3.7 months	PFS1, 5.5 months PFS2, 3.7 months
mPFS2/ mPFS1				67%	45%	67%

m, median; PFS1, progression-free survival period 1; PFS2, progression-free survival period 2.

Paper #26 3443599

CHARACTERIZATION OF THE EXTENSIVE HETEROGENEITY OF KIT/PDGFRA MUTATIONS IN PATIENTS WITH FOURTH-LINE ADVANCED GASTROINTESTINAL STROMAL TUMOR: GENOMIC ANALYSIS OF THE PHASE 3 INVICTUS STUDY

Sebastian Bauer[1], *Patrick Schöffski*[2], *Michael Heinrich*[3], *Suzanne George*[4], *John Zalcberg*[5], *Hans Gelderblom*[6], *César Serrano*[7], *Robin L. Jones*[8], *Steven Attia*[9], *Gina D'amato*[10], *Ping Chi*[11], *Peter Reichardt*[12], *Julie Meade*[13], *Vienna L. Reichert*[13], *Ying Su*[13], *Rodrigo Ruiz-Soto*[13], *Jean-Yves Blay*[14], *Margaret von Mehren*[15]

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Objective: KIT/PDGFRA mutations within the juxtamembrane (exon 11) and extracellular domain (exon 9) are early oncogenic events in gastrointestinal stromal tumors (GIST) and remain oncogenic drivers in the metastatic setting. Clonal evolution of additional mutations within the two kinase domains (exons 13, 14, 17 and 18) represent the major mechanism of resistance to KIT tyrosine kinase inhibitors (TKIs), and approved 2nd- and 3rd-line drugs inhibit only a limited spectrum of resistance mutations. Ripretinib is a switch-control TKI designed to broadly inhibit mutant KIT and PDGFRA kinases. Ripretinib was recently approved for patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors (including imatinib) based on the pivotal INVICTUS trial. Baseline tumor and plasma samples were collected to investigate the genomic heterogeneity of resistance in the well-defined patient cohort (≥4th-line) of the INVICTUS trial.

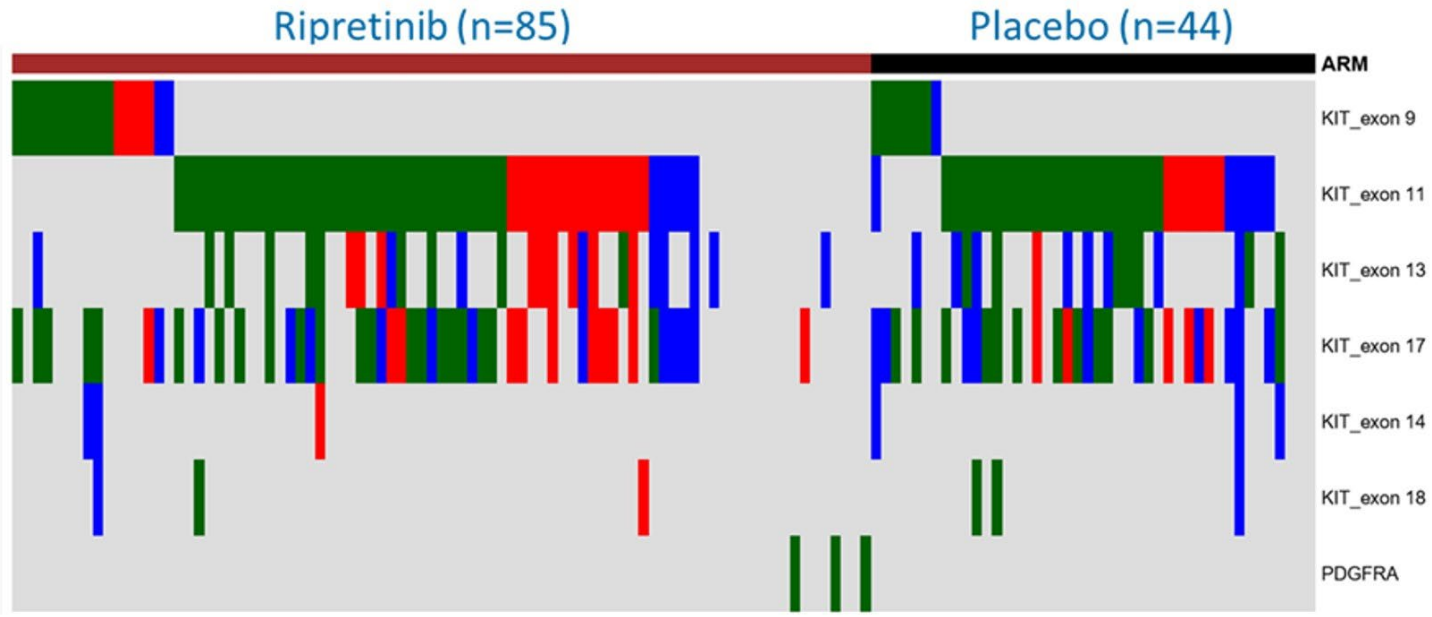
Methods: Tumor biopsies obtained prior to study entry were sequenced using a next-generation sequencing (NGS) panel that includes 324 genes. Liquid biopsies (plasma circulating tumor DNA [ctDNA]) were collected predose on Cycle 1 Day 1 and profiled using an NGS liquid biopsy assay (73 genes). Both assays included full coverage of the *KIT* and *PDGFRA* genes.

Results: Overall, 129 patients were randomized and tumor and plasma samples were submitted in 128 and 122 cases, respectively. Genotyping of the tumor tissue revealed a typical distribution of primary mutations with a majority of exon 11 mutant GIST (67%) followed by exon 9 (18%), exon 13 or 17 (4%), and PDGFRA exon 18 mutations (3%) (**Figure**). A proportion of patients (9%) lacked a KIT/PDGFRA mutation. Among patients with KIT exon 9 or 11 mutations, 67% of samples had at least 1 secondary resistance mutation and 9% had 2 or more exons affected by secondary resistance mutations. Notably, primary KIT/PDGFRA mutations were found in plasma in 78% of patients. Plasma sequencing revealed secondary resistance mutations in at least 1 exon in 70% of KIT/PDGFRA primary mutant GIST and 24% of patients had 2 or more exons affected. Patients with KIT exon 9 primary mutations exhibited fewer resistance mutations than those with exon 11 primary mutations. In 3 PDGFRA mutant cases, only a single PDGFRA mutation in exon 18 was detected. In aggregate, combined tumor and plasma biopsies allowed detection of resistance mutations in 73% of patients. Resistance mutations were detected in up to 4 exons (KIT exon 13/14/17/18 mutation) within a single patient.

Conclusion: This is the largest retrospective dataset of tumor and plasma sequencing in a ≥4th-line setting in GIST. Combination of tumor and liquid biopsies increased the detection rate of resistance mutations. Our results illustrate the mutational landscape heterogeneity of resistance in patients with KIT/PDGFRA-mutated tumors previously treated with at least 3 lines of therapy, thus highlighting the need for therapies that are effective against a broad spectrum of mutations.

Figure. Heterogeneity of KIT/PDGFRA mutations in tumor and liquid biopsy of patients with 4th-line advanced GIST.

Each column represents a single patient. Green indicates mutation in both tumor biopsy and ctDNA; red indicates mutation in tumor biopsy only; blue indicates mutation in ctDNA only.



9:00 am - 10:00 am – Session 10 –

ADVANCES IN ANGIOSARCOMA, PECOMA, AND CLEAR CELL SARCOMA

Paper #27 3460221

GENOMIC LANDSCAPE OF ANGIOSARCOMA: A TARGETED AND IMMUNOTHERAPY BIOMARKER ANALYSIS OF 143 PATIENTS

Andrea Espejo-Freire[1], *Andrew Elliott*[2], *Yamac Akgun*[1], *Philippos A. Costa*[1], *Maryam Alasfour*[1], *Andrew Rosenberg*[1], *Julio Diaz-Perez*[1], *Gina D'amato*[1], *Ty K. Subhawong*[1], *Junaid Arshad*[1], *W. Michael Korn*[2], *Don Dizon*[3], *Margaret von Mehren*[4], *Moh'd Khushman*[5], *Atif Hussein*[6], *Kirsten Leu*[7], *Jonathan Trent*[1]
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Objective: Angiosarcoma (AS) is an uncommon highly aggressive sarcoma representing 3% of all STS. In advanced disease, initial responses to cytotoxic chemotherapy are common. However, the duration of response is limited, and the median OS is only 3 to 12 months. Targeted therapy has demonstrated minimal efficacy. Despite evidence of the upregulation of vascular specific receptor tyrosine kinases, VEGF blockade provides only a 2-3-month survival benefit. More recently, we reported a series of AS patients with a 71% response rate to immune checkpoint inhibitors (ICIs). However, predictive factors for immunotherapy (IO) response in angiosarcoma are in an early stage of development. Understanding distinct molecular drivers and the immune microenvironment may be crucial for predicting responses to ICIs and other novel agents. Herein, we performed a comprehensive molecular analysis to identify potential therapeutic agents, including IO, for patients with AS.

Methods: We retrospectively reviewed 143 AS tumors profiled by Caris Life Sciences from 2015-2019. Next-Generation Sequencing (NGS) enriched for 592 cancer-related whole-gene targets was performed on each tumor. Whole transcriptome sequencing (WTS) was performed on 53 tumors and used for microenvironment cell population (MCP)-counter analysis. Biomarkers potentially associated with response to IO (TMB-High [≥10/Mb], MSI-High, and PD-L1 [IHC ≥ 2+ and 5%]) were also analyzed. Molecular results were evaluated according to the primary tumor site. Statistical analyses were performed using Chi-square or Fisher's exact tests where appropriate. Benjamini & Hochberg adjusted p-value was used for multiple hypothesis testing.

Results: The median age was 67 (range 22-89), 61% were female, and 29% were classified as metastatic/recurrent. Potential IO-response biomarkers were present in 36.4% of cases (TMB-High in 26%, PD-L1+ 21.8%, MSI-High 0.7%). The most common genetic alterations were TP53 (29%), MYC amp (29%), ARID1A (17%), POT1 (16%), and ATRX (13%). Biomarkers were distinct according to the primary site. Head and Neck AS had the highest incidence IO-response markers: 65% of cases (n=28/43; p<0.0001, q=0.0149), TMB-High observed in 62.5% (n=25/40; p<0.0001). Additionally, TP53 mutations present in 50.0% (n=21/42; p=0.0004), POT1 in 40.5% (n=17/42; p<0.0001), and ARID1A in 33.3% (n=5/15; p=0.5875, q=1.0) were over-represented at this site. In breast AS, cell cycle pathway aberrations driven by MYC amplification were present in 63.3% (n=19/30; p<0.0001). Mutations in HRAS were present in 16.1% (n=5/31; p=0.0377) and PI3KCA in 16.1% (n=5/31; p=0.2352) of Breast AS patients. By the MCP-counter method, we identified four distinct immune classes based on microenvironment cell population abundance: Immune-High – B lineage high (13.2%), Vascularized – Endothelial cells high (24.5%), Immune-Desert (41.5%) and Heterogeneous – Moderate abundance (20.8%). Immune class signatures were evenly distributed among different primary sites. Interestingly, the Immune-High class had the lowest median TMB = 6 muts/MB (range 3-17).

Conclusion: Our findings suggest a differential angiosarcoma biology across primary sites. Head and Neck AS has more frequent markers of potential IO-response, as well as DNA-Damage repair alterations. Consequently, further prospective clinical trials for the use of IO in Head and Neck AS are warranted. The use of MCP-counter as an adjunctive predictive

method of IO-response needs further validation in prospective AS trials as it may help identify patients without classical IO-response markers that can potentially benefit from IO.

Moreover, Breast AS was enriched for MYC amplification, HRAS and PI3KCA alterations. Consequently, targeting these pathways in Breast AS appears biologically reasonable and needs further study. Finally, truncating mutations in ARID1A (which codes for part of SNF/SWI complex) were present in 17% of our cohort. There is a rationale for the use of EZH2 inhibitors in this scenario.

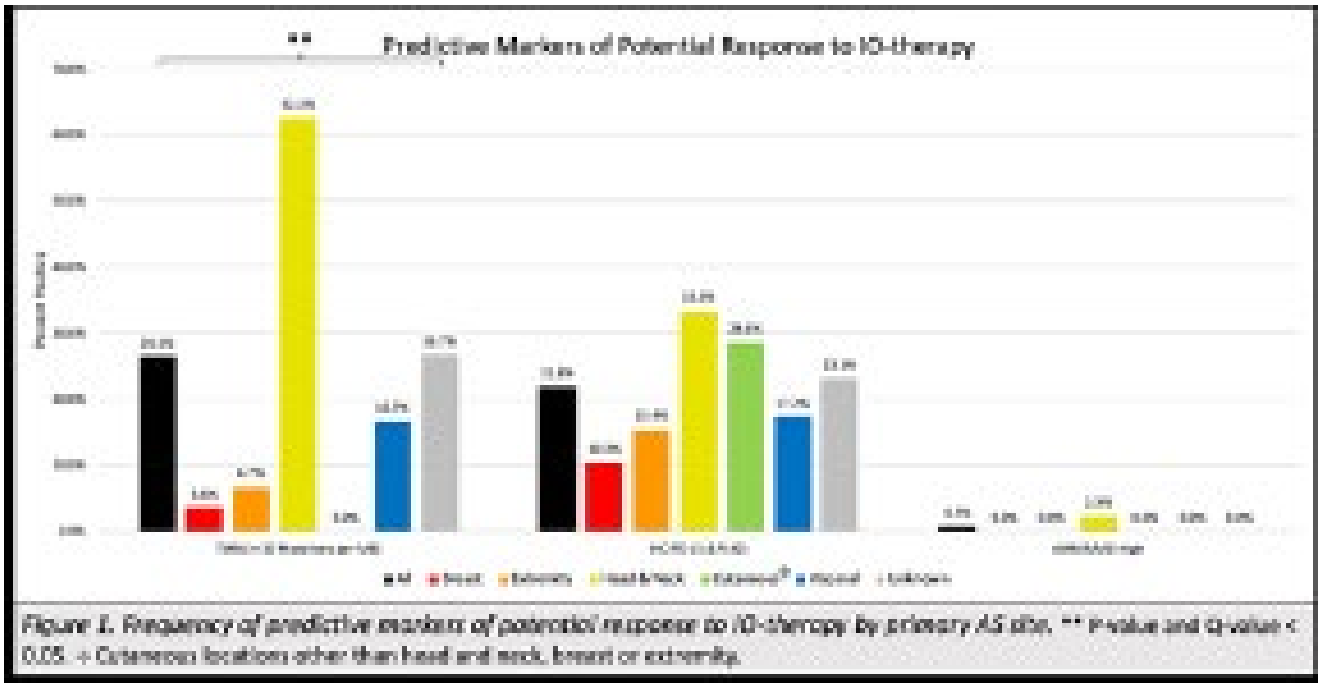

*Figure 1. Frequency of predictive markers of potential response to IO-therapy by primary AS site. ** P-value and q-value < 0.05. + Cutaneous locations other than head and neck, breast or extremity.*

Paper #28 3464567

THE PROTEOME LANDSCAPE OF SOFT TISSUE SARCOMAS DEFINES TWO FUNCTIONAL SUBGROUPS OF ANGIOSARCOMAS WITH DISTINCT SURVIVAL OUTCOMES

Jessica Burns[1], *Lukas Krasny*[1], *Christopher Wilding*[1], *Maggie Cheang*[1], *Robin L. Jones*[2], *Paul Huang*[1]
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Objective: We have undertaken comprehensive proteomic profiling of soft tissue sarcomas (STS) to identify new biological pathways and proteome-centric subtypes, as well as prioritise novel drug targets and discover prognostic biomarkers.

Methods: Comprehensive proteomic profiling of formalin-fixed paraffin-embedded tissue specimens from primary STS tumours was performed using mass spectrometry with 11-plex tandem mass tags. This generated quantitative proteomic profiles for 207 cases spanning 9 histological subtypes: undifferentiated pleomorphic sarcoma (UPS; n = 52), leiomyosarcoma (LMS; n = 48), synovial sarcoma (SS; n = 35), dedifferentiated liposarcoma (DDLPS; n = 31), epithelioid sarcoma (ES; n = 17), angiosarcoma (AS; n = 16), alveolar soft part sarcoma (ASPS; n = 4), desmoplastic small round cell tumour (DSRCT; n = 3), and clear cell sarcoma (CCS; n = 1).

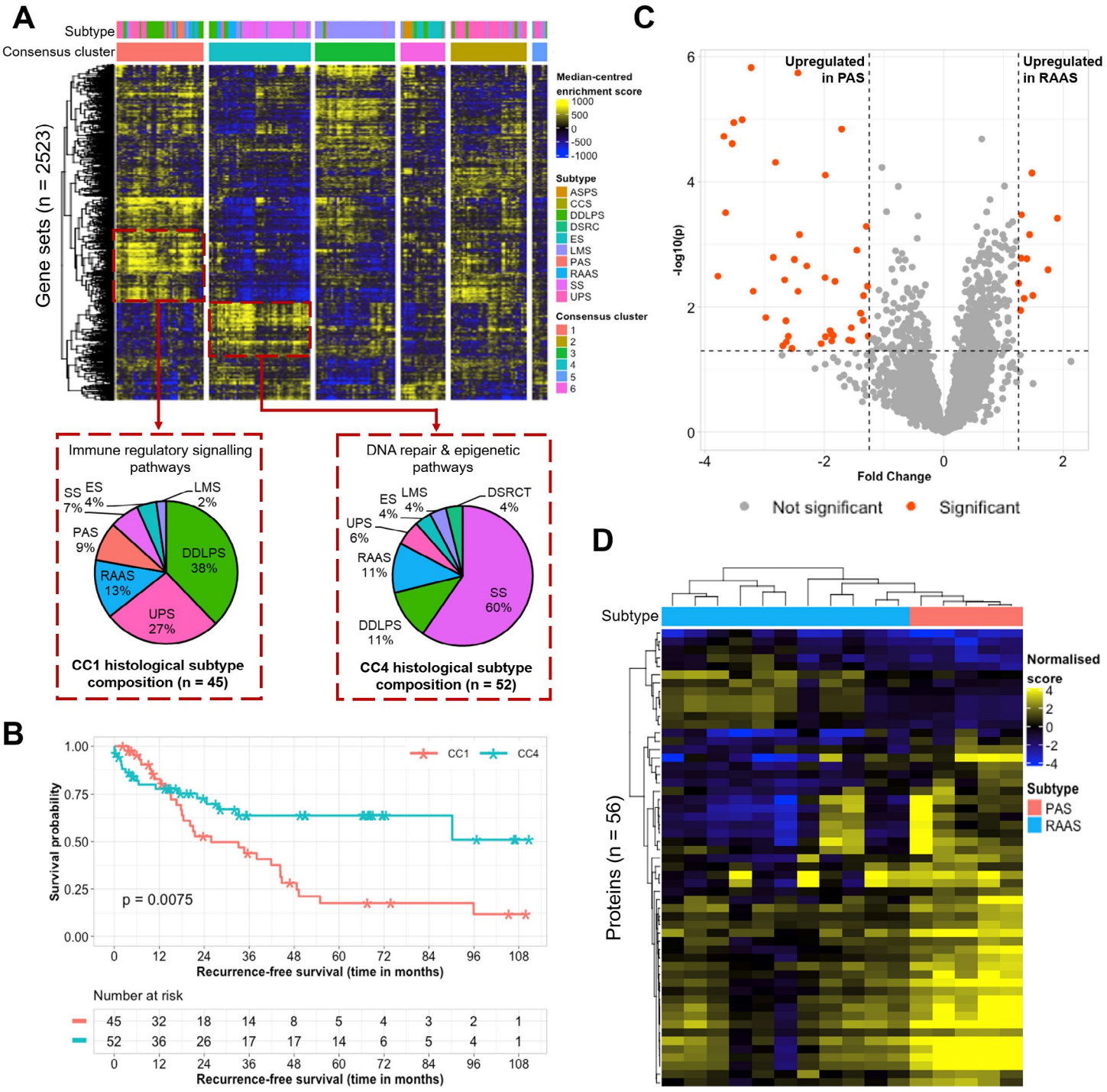
Differentially expressed proteins (DEP) were identified across subtypes by Significant Analysis of Microarrays (SAM) (q-value <0.01). 2523 Hallmark and Gene Ontology gene sets were tested for significant enrichment within DEPs using Gene Set Enrichment Analysis (GSEA). With the same gene sets, single sample GSEA (ssGSEA) was used to calculate pathway activity scores for each tumour. Consensus clustering (CC) of ssGSEAs was used to identify novel pan-subtype STS clusters. Differential overall survival (OS), recurrence-free survival (RFS) and metastasis-free survival (MFS) between the different clusters were estimated by Kaplan Meier Curves and hazard ratios were determined using univariable Cox regression analysis. To explore the molecular heterogeneity within AS, DEP between primary AS (PAS) and radiation-associated AS (RAAS) were determined with pre-specified cut-off (fold difference >1.25 and p <0.05), and the expression patterns were visualised by unsupervised hierarchical clustering.

Results: Comprehensive proteomic analysis identified 7896 proteins of which 3519 were quantified across all 207 cases. There were 2764 DEP identified across subtypes with histological subtype-specific protein signatures defined for LMS, SS and ASPS. CC of ssGSEA scores identified 6 functional subgroups with distinct biological pathways (Fig 1A). Within the cohort, the 16 AS cases had intrinsic biological heterogeneity and were grouped objectively by CC in two distinct functional subgroups of mixed histological subtypes (CC1 and CC4) (Fig 1A). CC1 contains 10 AS cases (5 PAS and 5 RAAS) and is enriched in immune regulatory signalling pathways while CC4 contains 6 AS cases (all RAAS) and is enriched in DNA repair and epigenetic pathways. Survival analysis showed that CC4 had a statistically significant superior RFS compared to CC1 (Fig 1B) with a hazard ratio of 0.77 for RFS (95% CI 0.63-0.94, p=0.009).

Comparative analysis of PAS (n=5, 4 breast, 1 scalp) versus RAAS (n=11, all breast) identified 56 DEP (>1.25 fold, p<0.05), with 45 and 11 proteins upregulated in PAS and RAAS respectively (Fig 1C). Over-representation analysis identified stress response pathways as upregulated in PAS compared to RAAS patients. A proteomic signature comprising of these 56 proteins was able to discriminate between PAS and RAAS (Fig 1D). Proteins significantly upregulated in PAS include several known cancer genes (MMP9, TGM2 and ITGB3) which are novel candidate targets for future drug development.

Conclusion: We have undertaken the first comprehensive proteomic analysis of STS which identified 2 functional subgroups containing AS (CC1 and CC4) with distinct survival outcomes. We have further developed a 56 protein signature that can discriminate PAS and RAAS and identified new drug targets for this disease of unmet need.

Figure 1. (A) Unsupervised hierarchical clustering of ssGSEA enrichment scores across 207 STS cases. Heatmap is split based on consensus clusters. Red boxes indicate upregulated ontologies and histological subtype composition of consensus cluster 1 (CC1) and consensus cluster 4 (CC4). (B) Recurrence-free survival analysis of patients in CC1 and CC4. P value determined by log-rank test. (C) Volcano plot of protein expression fold difference between PAS and RAAS for each of the 3519 protein in the proteomic dataset and their associated –log p value. Differentially expressed proteins (DEPs) shown in red (fold change >1.25 and p <0.05). (D) Unsupervised hierarchical clustering of DEPs in PAS and RAAS tumours.



Paper #29 3463014

LONG-TERM FOLLOW-UP FROM AMPECT, AN OPEN-LABEL PHASE 2 REGISTRATION TRIAL OF NAB-SIROLIMUS FOR PATIENTS WITH ADVANCED MALIGNANT PERIVASCULAR EPITHELIOID CELL TUMORS (PECOMA)

Andrew J. Wagner[1], *Vinod Ravi*[2], *Richard F. Riedel*[3], *Kristen Ganjoo*[5], *Brian A. Van Tine*[6], *Rashmi Chugh*[7], *Lee D. Cranmer*[8], *Erlinda M. Gordon*[9], *Jason L. Hornick*[10], *Heng Du*[10], *Berta Grigorian*[4], *Anita N. Schmid*[4], *Shihe Hou*[4], *Katherine Harris*[4], *David Kwiatkowski*[10], *Neil Desai*[4], *Mark Dickson*[11]
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Objective: Malignant perivascular epithelioid cell tumor (PEComa) is a rare, aggressive sarcoma, with no approved treatment. Cytotoxic chemotherapies have limited benefit in this patient population. Case reports suggest that the PI3K/AKT/mTOR pathway is activated in PEComa and mTOR inhibition may be efficacious in this disease. ABI-009 is a novel albumin-bound intravenous mTOR inhibitor with increased tumor uptake, increased mTOR target suppression and distinct pharmacokinetic profile versus oral mTOR inhibitors. The AMPECT trial is the first prospective study in advanced malignant PEComa (NCT02494570).

Methods: Patients with malignant PEComa were confirmed by central pathology review, and with measurable disease and ECOG 0 or 1 received *nab*-sirolimus (100 mg/m^2 IV, weekly, 2/3 weeks) until progression or unacceptable toxicity. Primary endpoint: objective response rate (ORR) by independent radiology review (IRR), assessed every 6 weeks (RECIST v1.1). Secondary endpoints: duration of response (DOR), progression-free-survival rate at 6 month (PFS6), median PFS and overall survival, and safety. Exploratory endpoints: investigator-assessed outcomes and mutational status. Here we report a 1 year follow-up after the primary analysis, which occurred when the last patient was treated for 6 months.

Results: A total of 35 patients were enrolled between Apr 2016 and Nov 2018, 34 were treated with at least one dose of *nab*-sirolimus, and 31 were evaluable for efficacy. The confirmed ORR by independent radiology review was 39%, all partial responses (PR, 12/31, 95% CI: 21.8, 57.8) at the primary analysis. One patient with a primary renal PEComa metastatic to the lungs and lymph nodes had a PR for 9.1 months that converted to a complete response, and the response is ongoing at 21.6+ months. Stable disease (SD) was the best response in 52% of patients (16/31, with 10/16 SD had SD ≥12 weeks), and 10% of patients had progressive disease (PD, 3/31).

Median duration of response (DOR) was not reached, with 67% responders continuing to respond 1 year after the primary data cutoff. The range of DOR was 5.6, 42.4+ months, with calculated median 25.2+ months and ongoing when censoring rules were ignored.

Median PFS was 8.9 months (95% CI: 5.5; not reached). At 6 months, 70% of patients remained progression free. At 12 and 24 months the progression free rate was 43%, both. Median OS has not been reached at the 1-year follow-up, as 25 of 34 treated patients were still alive, with OS rate at 6 months of 93% (95% CI: 75.5, 98.3), 89% at 12 months, and 69% at 24 months.

Twenty-five of 31 efficacy evaluable patients had tumor mutation profiling. Eight of 9 (89%) patients with a *TSC2* mutation achieved a response vs 2 of 16 (13%) without a *TSC2* mutation identified (P<0.001, Fisher's exact test). Most treatment-related AEs (TRAEs) were grade 1 or 2, and were manageable for long-term treatment. None were grade ≥4. The most common treatment-related AEs (TRAEs) of any grade were mucositis (79%), fatigue (59%), rash (56%), anemia/ nausea (47% each), diarrhea/weight loss (38% each), hyperglycemia (35%), and hypercholesterolemia/hypertriglyceridemia/ thrombocytopenia (32% each).

Conclusion: The AMPECT study met its primary endpoint with an independently assessed ORR of 39% and produced long-term durable responses. This encouraging response rate, durable responses, disease control, and manageable toxicities

suggested that *nab*-sirolimus appears safe and effective in the treatment of advanced malignant PEComa and represents an important new treatment option for these patients.

Paper #30 3465453

BEYOND THE FUSION: THE CLEAR CELL SARCOMA FUNCTIONAL GENOME

*Emanuele Panza[2], **Ben Ozenberger**[1], Krystal Straessler[3], Jared J. Barrott[4], Anne M. Boulet[5], Clint Mason[6], Alexander Lazar[7], Mario R. Capecchi[5], Kevin B. Jones[1]*
[1]Orthopaedics and Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, UNITED STATES; [2]Department of Medical and Surgical Sciences - DIMEC, University of Bologna, Bologna, ITALY; [3]School of Medicine, University of Utah, Salt Lake City, Utah, UNITED STATES; [4]College of Pharmacy, Idaho State University, Pocatello, Idaho, UNITED STATES; [5]Department of Human Genetics, University of Utah, Salt Lake City, Utah, UNITED STATES; [6]Department of Pediatrics, University of Utah, Salt Lake City, Utah, UNITED STATES; [7]Department of Pathology, MD Anderson Cancer Center, Houston, Texas, UNITED STATES

Objective: Clear cell sarcoma (CCS), a deadly malignancy in adolescents and young adults, remains genetically uncharacterized beyond the *EWSR1-ATF1* or *EWSR1-CREB1* fusion. We aimed to understand, through genome profiling of human tumors and novel mouse genetic models of CCS, what additional changes were present and capable of contributing to sarcomagenesis.

Methods: First, analysis of copy number alteration by single nucleotide polymorphism (SNP) array among a cohort of human clear cell sarcomas with archival specimens available identified recurrent changes. Second, sequencing of tumor exomes from mice expressing EWSR1-ATF1 from the *Rosa26* locus tested what additional changes were necessary to drive tumorgenesis in the model. Third, a new model driven by Cre-loxP-induced chromosomal translocation between *Ewsr1* and *Atf1* and also drove limited chromosomal instability was checked for copy number changes. Finally, the *Rosa26* model was used to test candidate alleles, suggested by the human tumor analysis, for contribution to sarcomagenesis.

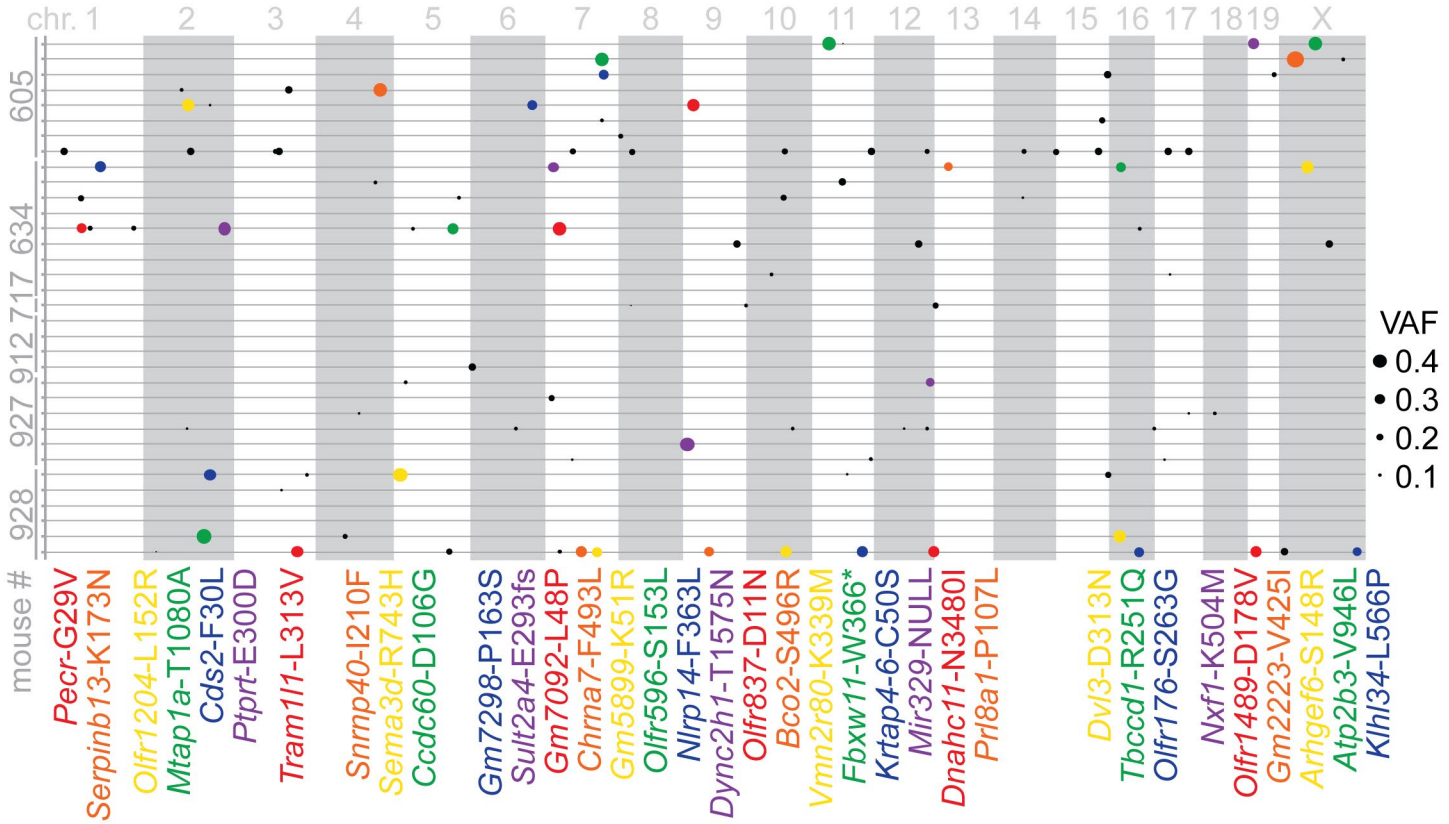
Results: Recurrent human CCS genome changes included the *MITF* and *CDKN2A* loci changes and chromosomes 7, 8, and 12q amplifications. Some CNAs were shared with Ewing sarcomas and desmoplastic round cell tumors, suggesting a relationship with the EWSR1 portion of the fusion oncoprotein. No additional changes were identified in the *Rosa26* exomes. Copy number changes in the mouse translocation model identified copy number alterations in mouse chromosome 15 regions that are syntenic to human chromosome 8. Testing of *Mitf*, and *Myc* in the Rosa26 model found each capable of contributing to sarcomagenesis, but may also change the character of tumorigenesis that results.

Conclusion: CCS tumors bear consistent copy number changes, most prominently amplifications of *MITF* and chromosomes 7 and 8 in a majority of tumors. The impact of *Mitf* on mouse clear cell sarcomagenesis is subtle, but detectable. The impact of *Myc* amplification, as a candidate for human chromosome 8 amplification, was capable of enhancing sarcomagenesis, but also changed the character of tumors appreciably, suggesting that other candidates may be more impactful from chromosome 8.

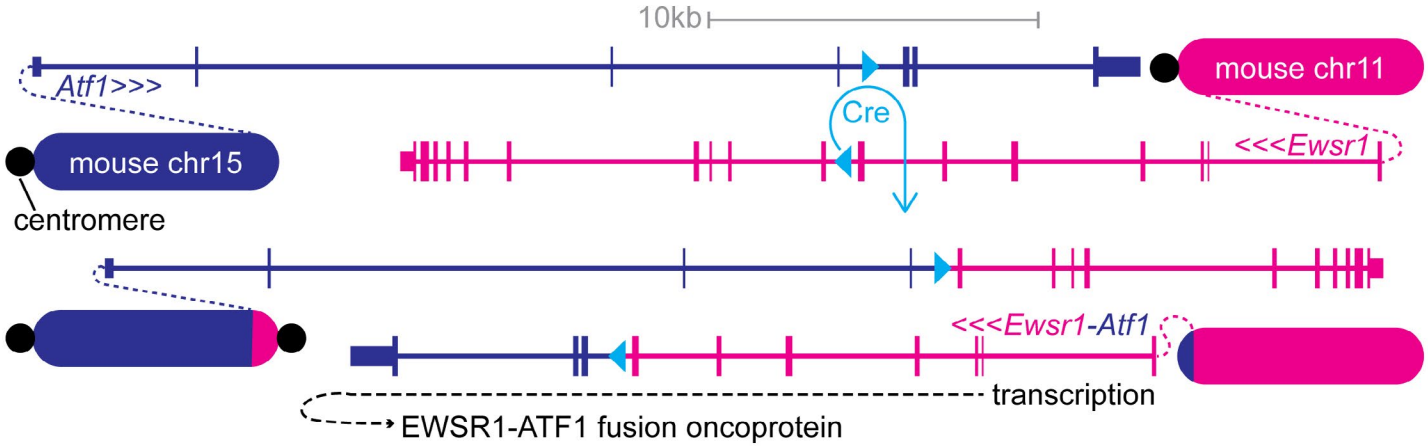
Recurrent Copy Number Alterations in Human CCS

CHROMOSOME/REGION/LOCUS	ALTERATION	PREVALENCE
chromosome 8	amplification	14 / 18
chromosome 7	amplification	11 / 18
MITF locus	amplification	10 / 18
CDKN2A locus	loss	5 / 18
chromosome 12 q arm	amplification	4 / 18

Exome sequencing of mouse clear sarcomas identified no recurrent mutations and few mutations of any kind in these tumors.



Schematic of the mouse induced-translocation model of clear cell sarcomagenesis by Cre-loxP-mediated translocation between chromosomes 11 and 15 to generate an *Ewsr1-Atf1* fusion.



11:30 am - 12:30 pm – Session 11 –

RHABDOMYOSARCOMA AND EWING SARCOMA

Paper #31 3443006

SURVIVAL OUTCOMES OF PATIENTS WITH LOCALIZED FOXO1 FUSION POSITIVE RHABDOMYOSARCOMA TREATED ON RECENT CHILDREN'S ONCOLOGY GROUP CLINICAL TRIALS

Christine M. Heske[1], *Yueh-Yun Chi*[2], *Rajkumar Venkatramani*[3], *Minjie Li*[2], *Michael Arnold*[4], *Roshni Dasgupta*[5], *Susan M. Hiniker*[6], *Douglas S. Hawkins*[7], *Leo Mascarenhas*[8]
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Objective: Recent reports have indicated that *FOXO1* status is the most significant factor impacting outcomes among patients with localized (clinical group I-III) rhabdomyosarcoma (RMS). However, the clinical factors influencing outcomes among a large group of patients with localized *FOXO1* FP tumors have not been examined previously. The aim of this analysis was to evaluate the clinical factors influencing survival outcomes in patients with localized *FOXO1* fusion positive RMS treated on three recent Children's Oncology Group (COG) clinical trials conducted between 1997 and 2013.

Methods: Patients with newly diagnosed, localized, confirmed *FOXO1* fusion positive RMS who were enrolled on three COG clinical trials for RMS (D9602, D9803, and ARST0531) were included in the analysis**.** Outcomes were analyzed using the Kaplan-Meier method to estimate event-free survival (EFS) and overall survival (OS) distributions with an event defined by relapse/progression, second malignancy, or death, whichever occurred first. Differences between survivalcurves were compared using the log-rank test. A Cox proportional hazards regression model was used to adjust comparisons of the EFS and OS by including prognostic factors that were significant in the univariate analysis.

Results: We identified 269 eligible patients with localized *FOXO1* fusion positive RMS, nearly all of whom (n=256; 95%) were treated either on D9803 or ARST0531. *PAX* fusion data was available for the majority of tumors (n=243; 90%), with *PAX3-FOXO1* fusions identified in most cases (n=192; 71%). For all patients, the estimated 4-year EFS and OS were 53% (95% CI: 47%-59%) and 69% (95% CI: 63%-74%), respectively. Univariate analysis revealed that a number of known favorable clinical characteristics at diagnosis including age between 1 and 9 years, complete surgical resection, tumor size $\leq$ 5 cm, favorable tumor site, absence of lymph node involvement, and *PAX7-FOXO1* fusion were associated with improved outcomes. Multivariate analysis demonstrated that tumor size and *FOXO1* fusion partner significantly correlated with OS. Patients with large tumors (> 5 cm) experienced worse OS compared to those with smaller tumors (p=0.0085), and patients with *PAX3-FOXO1* fusion tumors had inferior OS, compared to those with *PAX7-FOXO1* fusion tumors (p=0.032). For EFS, multivariate analysis identified both age and tumor size as independent prognostic factors. Patients diagnosed younger than 1 year or 10 years or older had significantly poorer EFS compared to the group diagnosed between 1 and 9 years of age (p=0.014), as did those with large tumors (> 5 cm) (p=0.006). Patients who were both 10 years or older and had primary tumors > 5 cm experienced substantially worse outcomes, with 4-year EFS 31% (95% CI, 19%-43%) compared to patients with just one of these adverse features (p<0.0001).

Conclusion: In the largest cohort of patients with localized fusion positive RMS to date, we confirmed the more favorable prognosis of patients with *PAX7-FOXO1* fusions. Furthermore, we found that older patients with large tumors have similar outcomes to stage 4, clinical group IV RMS and could be included on future COG high-risk clinical trials.

Paper #32 3461602

ALVEOLAR RHABDOMYOSARCOMA HAS SUPERIOR CLINICAL RESPONSE RATES TO VINORELBINE COMPARED TO EMBRYONAL RHABDOMYOSARCOMA IN PATIENTS WITH REFRACTORY OR RELAPSED DISEASE

Wendy Allen-Rhoades[1], *Philip Lupo*[1], *Michael Scheurer*[1], *Yueh-Yun Chi*[2], *John Kuttesch*[3], *William H. Meyer*[4], *Rajkumar Venkatramani*[1], *Leo Mascarenhas*[2]

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Objective: Patients with alveolar rhabdomyosarcoma (ARMS) have inferior outcomes compared to patients with embryonal rhabdomyosarcoma (ERMS) and more effective chemotherapy options are needed for these patients. Vinorelbine is a semi-synthetic vinca alkaloid that has clinical activity in relapsed rhabdomyosarcoma (RMS) when used alone or in combination with cyclophosphamide. The goal of our study was to evaluate whether RMS histology subtype influences response rate to vinorelbine alone or in combination.

Methods: Five Phase 2 trials that enrolled RMS patients were included in the meta-analysis. Two studies evaluated vinorelbine alone (Casanova 2002, Kuttesch 2009), two studies evaluated vinorelbine in combination with low dose oral cyclophosphamide (Casanova 2004, Minard-Colin 2012) and one study evaluated vinorelbine and intravenous cyclophosphamide in combination with temsirolimus or bevacizumab (Mascarenhas 2019). All RMS patients had relapsed or refractory disease and had received at least one prior therapy. Response was reported according to RECIST1.1 and was defined as a complete or partial response. Response data was obtained from published results or from trial principal investigator. RMS NOS patients were grouped with ERMS patients for this analysis. Summary estimates comparing differences between ARMS and ERMS response rates were generated using a random-effects model to account for heterogeneity among the studies. Analyses were conducting using the meta commands in Stata v16 (College Station, TX).

Results: 156 enrolled patients evaluable for response were included in the meta-analysis, 85 ARMS, 64 ERMS and 7 RMS-NOS. The combined effect generated from the random-effects model demonstrated a 41% increase (p = 0.001, 95%CI; 0.21-0.60) in response to vinorelbine as a single agent or in combination in patients with ARMS compared to patients with ERMS (Figure 1). There was no significant difference in the rate of progressive disease between patients with ARMS compared to ERMS (p=0.1, 95%CI; -0.26-0.02) (Figure 2).

Conclusion: Vinorelbine is an active agent for the treatment of relapsed or refractory RMS and a meta-analysis of Phase 2 studies shows that radiographic responses in patients with ARMS were significantly higher compared to patients with ERMS or RMS-NOS. These data support further investigation of vinorelbine in newly diagnosed patients with RMS particularly those with ARMS.

Figure 1: The combined effect generated from the random-effects model demonstrated a 41% increase in response to vinorelbine or vinorelbine containing regimens for patients with ARMS compared to patients with ERMS.

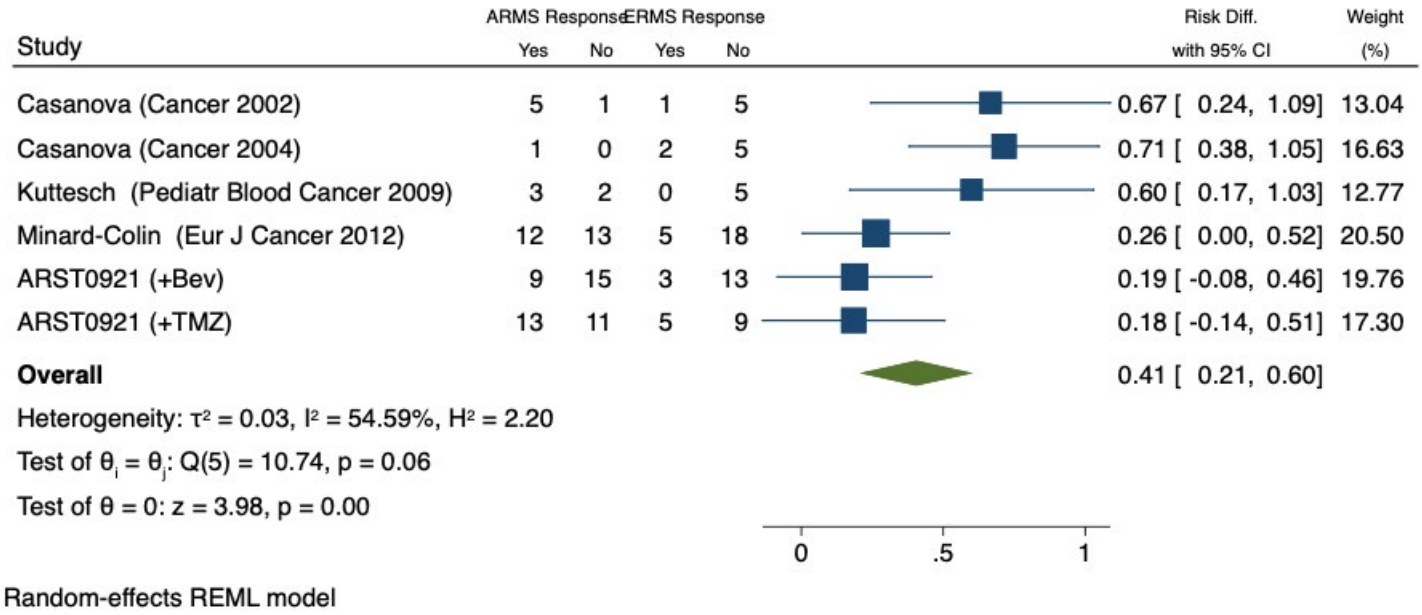
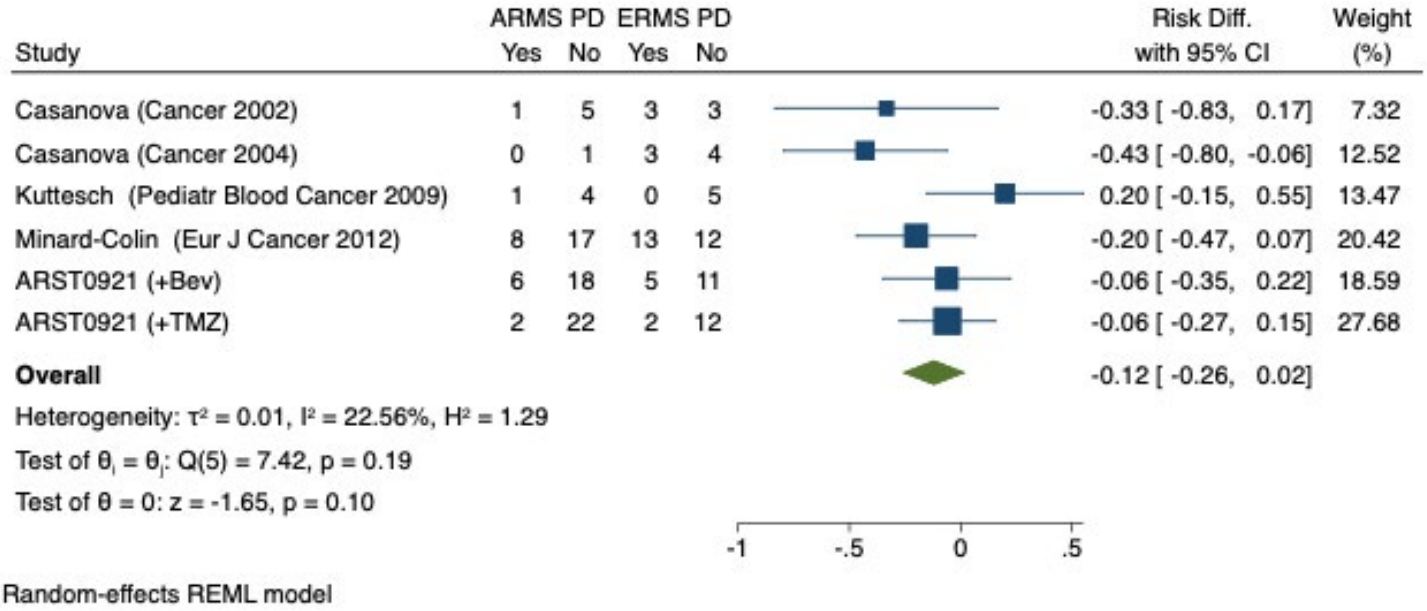


Figure 2. There was no significant difference in progressive disease for patients with ARMS compared to ERMS when treated with vinorelbine or vinorelbine containing regimens in the meta-analysis.



Paper #33 3457806

THE ROLE OF DLK1 IN FUSION-NEGATIVE RHABDOMYOSARCOMA

Margaret B. Nagel[1], *Matthew R. Garcia*[1], *Mark E. Hatley*[1]
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Objective: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and consists of two major histologic subtypes, alveolar rhabdomyosarcoma (ARMS) and embryonal (ERMS). ERMS tumors are fusion negative and genetically heterozygous with a subset likely driven by RAS family mutations and large subset without know drivers. We sought to further explore the molecular underpinnings in FN-RMS specifically looking at the paternally imprinted gene, delta like homolog 1 (DLK1). DLK1 participates in muscle formation as a single nucleotide polymorphism at the callipyge locus deregulates *DLK1* expression resulting in skeletal muscle hypertrophy. DLK1 is one of the highest expressed genes in our laboratory's genetically engineered mouse FN-RMS model. Given the role of DLK1 in skeletal muscle hypertrophy, we hypothesize that DLK1 plays a role in FN-RMS.

Methods: Mouse breeding: *Dlk1*^{flox} mice bred to aP2-Cre;Smo$^{M2/+}$ mice (AS) to give rise to wild-type *Dlk1* (ASDlk1^{WT}), hetero- and homozygous conditional knockout animals (ASDlk1^{cHet} and ASDLK1^{cKO}, respectively). For Kaplan-Meier tumor free survival mice were observed from birth then ASDlk1^{WT} sacrificed when showing signs of obvious tumor burden or distress and ASDLK1^{cKO} mice confirmed to be tumor free at necropsy. Cell lines: SMS-CTR (Rene Galindo, UT Southwestern), RD (CCL-136), JR1(Gerard Grosveld, St. Jude), Mast 153 (generated by Hatley lab).

Gene expression: Total RNA isolated using miRNEasy mini kit (#217004, Qiagen). Reverse transcription performed with Superscript III Firststrand Synthesis with random hexamer primers (Invitrogen). Real-time PCR was performed with SYBR primers or Taqman probes. Relative expression by qRT-PCR was quantified using DDC_T method normalized to *18S* ribosomal RNA and expressed relative to scramble control.

siRNA: MAST 153 cells were transfected with 20 nM of negative control or DLK1 siRNA (IDT) using RNAiMax (Invitrogen). 20,000 cells plated in 96 well plate in quadruplicate and proliferation monitored by live cell imaging (IncuCyte).

shRNA: Lentiviruses were generated using modified pLKO plasmids to express shRNA to *DLK1* or scramble control with puromycin resistance gene and packaged in 293T cells. Viral containing supernatant was used to transduce RMS cells that were maintained in 0.25 mg/mL of puromycin. RNA was isolated and gene expression determined after 72H.

Results: Our previously described FN-RMS murine model (aP2-Cre;Smo$^{M2/+}$) results from the activation of a conditional, constitutively active Smoothened (Smo^{M2}) allele by Cre recombinase expressed from the adipose protein 2 (aP2) promoter. We generated ASDlk^{WT}, ASDlk^{cHet}, and ASDlk^{cKO} compound mutant mice by breeding and monitored tumor formation. All of the ASDlk1^{WT} mice develop tumors while only 2 of 18 ASDlk^{cKO} animals developed tumors resulting from incomplete Cre-mediated recombination based upon the presence of Dlk1 gene expression in tumor cells. DLK1 is expressed in human FN-RMS cell lines with highest expression in MAST153, followed by RD, SMS-CTR, and JR1. We leveraged these cells lines for gain- and loss-of-function experiments to determine the role of DLK1 in FN-RMS. Knockdown of DLK1 expression with siRNA in MAST153 cells reduced *DLK1* expression and resulted in decreased cell proliferation via live cell imaging. The transient siRNA knockdown was confirmed with lentiviral shRNA knockdown of DLK1.

Conclusion: *Dlk1* deletion completely abrogates tumor formation in the *aP2-Cre;SmoM2* murine FN-RMS model indicating that DLK1 is critical for tumor initiation. The role of DLK1 in tumor promotion and maintenance remains unclear although early work has shown that with a knockdown of DLK1 in high expressing human FN-RMS cell lines decreased proliferation and cell viability. Ongoing studies leveraging human cell lines and patient derived xenografts will further elucidate the role of DLK1 in tumor promotion, maintenance and underlying molecular mechanism in rhabdomyosarcoma.

Paper #34 3435189

STRUCTURE-FUNCTION MAPPING REVEALS NOVEL REGION OF FLI CRITICAL FOR EWS/FLI ACTIVITY IN EWING SARCOMA

Megann Boone[1], *Cenny Taslim*[1], *Julia Selich-Anderson*[1], *Jesse Crow*[1], *Emily R. Theisen*[1], *Iftekhar Showpnil*[1], *Stephen Lessnick*[1]
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Objective: Ewing sarcoma (ES) is the second most common bone cancer in pediatric and AYA patients. Despite side effects, a strong chemotherapy and radiotherapy regimen, combined with surgery, has remained the standard of care for half a century. To overcome a lack of advancement in treatment, it is critical to understand the fundamental biology that drives Ewing sarcomagenesis to reveal potential new therapeutic vulnerabilities. ES is primarily driven by a sole chromosomal translocation that encodes a new fusion oncoprotein: EWS/FLI. This protein contains the DNA-binding domain (DBD) of the transcription factor FLI. Although fundamental for disease formation, extensive research on the contributions of FLI to EWS/FLI activity is largely absent in the field. Our goal is to complete structure-function mapping of FLI to determine how individual domains of the protein contribute to oncogenic roles of EWS/FLI and ES development.

Methods: Several different versions of EWS/FLI were created using cDNA constructs by mutating the regions of FLI contained in each. A ES cellular model was used to test functionality of these constructs. A variety of molecular biology and sequencing techniques were used to establish structure-function relationships, including luciferase reporter assays, soft agar assays, RNA-seq, CUT&RUN-seq, and ATAC-seq.

Results: Through various *in vivo* experiments, we have revealed that EWS/FLI containing only the DBD (EF DBD) maintains the ability of the protein to bind DNA and alter chromatin state. These properties are essential to the regulatory properties of transcription factors, but surprisingly, EF DBD is unable to regulate gene expression or drive oncogenic transformation in cells. Studies to determine what crucial regions EF DBD lacks to retain full activity have revealed a region just outside of the FLI DBD that plays an essential role in protein-protein interactions, which are necessary to mediate oncogenic transformation in ES cells.

Conclusion: Ultimately, we have isolated crucial regions of EWS/FLI that are essential for ES disease formation. Identification of novel regions of FLI essential for the oncogenic activity of EWS/FLI has clear utility moving forward in several ways: Known structures of FLI bound to DNA will enable the design of targeted small molecules to inhibit activity associated with this crucial region. Comparison of wild-type and mutant versions of this region can reveal loss of activity that is essential for ES formation, whether that be protein partners that enable chromatin conformation changes or transcriptional regulation. We believe these basic science findings do have the potential to contribute to the field in a significant way.

Paper #35 3464969

TK216 PHASE 1 STUDY IN METASTATIC, RELAPSED/REFRACTORY EWING SARCOMA

Joseph A. Ludwig[2], *Noah Federman*[4], *Peter Anderson*[10], *Margaret Macy*[3], *Lara E. Davis*[7], *Richard F. Riedel*[5], *Najat C. Daw*[2], *Jodi Muscal*[8], *Ravin Ratan*[2], *Jeffrey Toretsky*[6], *Xen Ianopulos*[1], *Frank Hsu*[1], *James Breitmeyer*[1], *Paul Meyers*[9]
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Objective: Ewing Sarcoma (ES) is a rare pediatric cancer with poor prognosis and high unmet need, and very few treatment options in the relapsed/refractory setting. Chimeric oncoproteins encoded by fusions of the EWS gene and one of five different ETS transcription factors are dominant drivers of the disease. TK216 was designed to bind ETS proteins directly, disrupt protein interactions, inhibit transcription factor function and cause apoptotic cell death. Notably, TK216 plus vincristine was shown to exert synergistic activity (Zollner 2017). Here, we report the results of the Phase 1 trial of TK216 in ES.

Methods: TK216 was administered by continuous IV infusion to adult and pediatric patients with relapsed / refractory ES in a Phase 1 study using a 3+3 design. Dosing duration of 7 days was later extended to 10 and 14 days, with a 14-day break to complete a cycle. DLT was evaluated during Cycle 1, and efficacy was evaluated after completion of Cycle 2. Vincristine could be added to treatment after Cycle 2.

Results: Thirty-two patients were enrolled into 9 dose and schedule escalation cohorts of TK216 ranging from 18 to 288 mg/m^2/day. The MTD for the 14-day infusion was 200 mg/m^2/d, which was selected as the recommended Phase 2 dose (RP2D). Treatments were manageable with DLTs of neutropenia/febrile neutropenia, and other AEs of thrombocytopenia, anemia and fatigue. As of the data cut (May 11, 2020), nine pts have had treatment in the expansion cohort with TK216 at the RP2D plus vincristine. No new toxicities were noted except neurotoxicity due to vincristine. Eleven patients with evaluable data were treated with the RP2D, 3 in the final dose escalation cohort and 8 in the expansion cohort, as of May 11, 2020. Observed efficacy was partial response (PR) 18% (2/11), stable disease 45% (5/11), for an overall clinical benefit rate of 64% (7/11). 3 of the patients experienced PD before reaching Cycle 2 evaluation (overall PD 36% (4/11). The two clinical responses were notable. One patient had a PR with a regression of all target lung lesions after 2 cycles of TK216 alone. After 6 months of TK216 +/- vincristine therapy, a small residual lesion was removed, for a surgical CR, now continuing for 14+ mos. A second patient had a PR with 90% reduction of target lung lesions by RECIST 1.1 after 2 cycles of TK216 plus vincristine. Pharmacokinetics were consistent across all phases of the study, with a half-life of 8 to 12 hours across the various doses, and plasma levels of TK216 appeared to reach steady state by day 4 of the continuous IV infusion.

Conclusion: TK216 was well tolerated and showed encouraging early evidence of anti-tumor activity in a patient population with limited or no treatment options.

12:30 pm - 1:30 pm

– Session 12 –

LOCALLY AGGRESSIVE MESENCHYMAL TUMORS: DESMOID TUMOR, DIFFUSE-TYPE GIANT CELL TUMOR

Paper #36 3465367

WEEKLY NAB-PACLITAXEL FOR PROGRESSIVE OR SYMPTHOMATIC DESMOID TUMORS: A MULTICENTER SINGLE ARM PHASE II TRIAL FROM THE SPANISH GROUP FOR RESEARCH ON SARCOMA (GEIS)

Javier Martin-Broto[1], *Nadia Hindi*[1], *Andres Redondo*[2], *Jose Manuel Morales*[3], *David Marcilla*[4], *Claudia Valverde*[5], *Pablo Luna*[6], *Robert D. Beveridge*[7], *Javier Martinez-Trufero*[8], *Jose Antonio Lopez-Martin*[9], *Virginia Martinez*[2], *Antonio Gutierrez*[10], *Antonio Lopez-Pousa*[11]

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Objective: Desmoid tumors (DT) are locally aggressive neoplasms, which can significantly impact on patients' quality of life and function. Systemic therapy can be considered in cases with progressive disease or in symptomatic patients. Previously described regimens such as methotrexate-based schemes are usually administered during long periods. This phase II trial explores the activity of short-course of weekly nab-paclitaxel in DT.

Methods: Adult patients with clinically and/or radiologically progressive DT received 3 cycles of nab-paclitaxel (125 mg/m2 days 1,8,15 every 28 days in patients > 21 years; 240mg/m2 days 1,8,15 every 28 days in patients aged 18-20 years). Primary combined end-point was overall response rate (ORR) by RECIST 1.1 and the clinical benefit rate (CBR) with pain improvement in at least 2 points based on Brief Pain Inventory (BPI) scale. H0= ORR 20% or CBR 25%; H1= ORR 40% or 50% CBR. Central pathology and radiological review were mandatory.

Results: From May 2017 to September 2019, 40 patients were enrolled in 8 centers: 26 Female/14 Male, median age at study entrance 38.5 years (18-77), site of disease (limbs in 14/40; trunk wall in 12/40, abdominal cavity 9/40, head and neck 5/40). Reason of inclusion was: RECIST progression in 13/40 (32.5%) patients, symptomatic/functional progression in 12/40 (30%) and both RECIST and pain in 15/40 (37.5%). All but 1 patients completed therapy (1 patient stopped due to allergic reaction after 1 cycle). ORR by RECIST (central radiological review) was 20.5% (8/39 evaluable patients had a partial response-PR; 30/39 (76.9%) stable disease-SD (in 19/39 there was shrinkage), 1/39 (2.5%) progressive disease-PD. Median worst pain at baseline was 6.5 (0-10) and median worst pain during therapy was 2 (0-6), with a median reduction in 4 points (0-8). 32/40 (80%) pts experienced at least reduction in 2 points in worst pain. 4 patients had G3 toxicities (G3 neutropenia in 2 cases, G3 mucositis in 1 case, G3 peripheral neuropathy). There were no G4 toxic effects. With a median of FU of 18 months, there were 2 PD, 6 SP and 2 both, PD and SP. Neck and proximal upper-extremity sites had worse 18month-PFS: 24% vs 86% in other locations ($p< 0.001$).

Conclusion: Short- course nab-paclitaxel was safe and active in this cohort of DT, with 80% of patients having clinical improvement and 20.5% experiencing a radiological response. In patients with DT in neck or proximal upper extremity this regimen was related with less efficacy in terms of 18 month-PFS.

Paper #37 3459474

ASSOCIATION OF CTNNB1 MUTATION SUBTYPES WITH RESPONSE TO SYSTEMIC THERAPY IN PATIENTS WITH DESMOID TUMORS: A MULTI-INSTITUTIONAL RETROSPECTIVE STUDY

Michael J. Nathenson[1], *Neeta Somaiah*[2], *Robert Hsu*[3], *Peter DeMaria*[3], *Heath Catoe*[3], *Karan Malik*[1], *Christy Harris*[1], *Ty K. Subhawong*[4], *Behrang Amini*[5], *Jyothi P. Jagannathan*[6], *Marta Braschi-Amirfarzan*[6], *Kevin Sweet*[4], *Katharina Feister*[4], *Junxiao Hu*[7], *Jamie Sheren*[8], *Andrew Rosenberg*[9], *Alexander Lazar*[10], *Ravin Ratan*[2], *Vinod Ravi*[2], *Shreyaskumar Patel*[2], *Robert Maki*[12], *Pasquale Benedetto*[3], *Jonathan Cohen*[3], *Jonathan Trent*[3], *Breelyn A. Wilky*[11]
[1]*Medicine, Dana Farber Cancer Institute, Boston, Massachusetts, UNITED STATES;* [2]*Medicine, MD Anderson Cancer Center, Houston, Texas, UNITED STATES;* [3]*Medicine, Sylvester Comprehensive Cancer Center University of Miami, Miami, Florida, UNITED STATES;* [4]*Radiology, University of Miami School of Medicine, Miami, Florida, UNITED STATES;* [5]*Radiology, MD Anderson Cancer Center, Houston, Texas, UNITED STATES;* [6]*Radiology, Dana Farber Cancer Institute, Boston, Massachusetts, UNITED STATES;* [7]*Biostatistics, University of Colorado School of Medicine, Aurora, Colorado, UNITED STATES;* [8]*Pathology, University of Colorado School of Medicine, Aurora, Colorado, UNITED STATES;* [9]*Pathology, University of Miami School of Medicine, Miami, Florida, UNITED STATES;* [10]*Pathology, MD Anderson Cancer Center, Houston, Texas, UNITED STATES;* [11]*Medicine, University of Colorado School of Medicine, Aurora, Colorado, UNITED STATES;* [12]*Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, UNITED STATES*

Objective: Desmoid tumors (DTs) exhibit unpredictable behavior; while many DTs are indolent or spontaneously regress, some are prone to multiple recurrences leading to patient morbidity and mortality. Cytotoxic chemotherapies including doxorubicin-based regimens, methotrexate/vinblastine, and sorafenib are among the most effective treatments for progressive DTs but are associated with toxicity. Prior studies suggest that patients with *CTNNB1* S45F mutations are more likely to recur after resection compared to *CTNNB1* T41A mutations. We established a multi-institutional dataset of DT patients to evaluate whether *CTNNB1* mutation subtype correlated with responses to systemic therapies.

Methods: We established a REDCAP database across four institutions: MD Anderson Cancer Center, University of Miami (UM), Mount Sinai Medical Center, and Dana-Farber Cancer Institute (DFCI). Under individual institutional IRB protocols, DT patients were retrospectively identified and clinical data, including mutation testing, treatment history, and radiographic responses were abstracted. Archival tissue was requested for UM and DFCI patients without previous mutation testing. Tissue was analyzed by Sanger sequencing for *CTNNB1* mutations, with next generation sequencing for *APC* or *CTNNB1* mutations in Sanger-negative specimens. When available, radiographic scans were re-reviewed by fellowship trained radiologists blinded to treatments to quantify RECIST 1.1 responses. In addition to RECIST radiographic progression-free survival (rPFS), we determined clinical PFS (cPFS), time-to-next-treatment, and overall survival (OS). PFS and OS were estimated using Kaplan-Meier method and compared using log-rank test. Cox proportional hazard regression models were used to estimate hazard ratios with 95% confidence intervals to determine impact of mutation status, treatment regimen, and DT location while adjusting for other covariates. Due to low patient numbers, Cox analysis was only performed for 1st and 2nd line treatments. Time to 2nd line therapy was included as a covariate in 2nd line analysis to adjust for biologic variation among DT patients. PFS for different treatments was also summarized by mutation subtype across all lines of therapy with descriptive intent. Funding provided by the Desmoid Tumor Research Foundation.

Results: We identified 309 DT patients, with 259 evaluable for at least one specified clinical outcome. Patients received a total of 707 treatment lines, ranging from 1-10 treatments per patient; 43% of patients received ≥ 3 treatments. Mutation testing was obtained in 177 patients (68%), identifying T41A (n=68), S45F (n=45), S45P (n=5) and *APC* (n=11) mutations, with 41 patients testing negative or with alternate mutations. OS was significantly worse in patients with *APC* mutations relative to T41A, S45F, or other mutations (p=0.028), and for mesenteric/intraabdominal and other location relative to extremity/trunk (p=0.004). No mutation group was associated with worse cPFS across all 1st or 2nd line therapies. In multivariate analysis, *APC* mutation status was associated with progression (HR 4.93, p=0.026), whereas doxorubicin/dacarbazine (ADIC) (HR 0.32, p=0.023) and liposomal doxorubicin (HR 0.39, p=0.047) treatment were associated with improved 1st line cPFS (Table 1). Across all treatment lines, no significant differences in cPFS were observed with different systemic therapies by mutation, though a trend towards improved cPFS was observed with sorafenib therapy in S45F mutated DTs relative to T41A mutations (Figure 1).

Conclusion: Cytotoxic chemotherapies retain significant clinical activity against DTs regardless of mutation subtype. An observed trend towards improved outcomes with sorafenib in S45F mutant DTs warrants further prospective investigation. *APC* mutations and mesenteric/intraabdominal DT location remain useful prognostic factors to identify higher risk patients who may warrant more intensive surveillance or earlier initiation of chemotherapy.

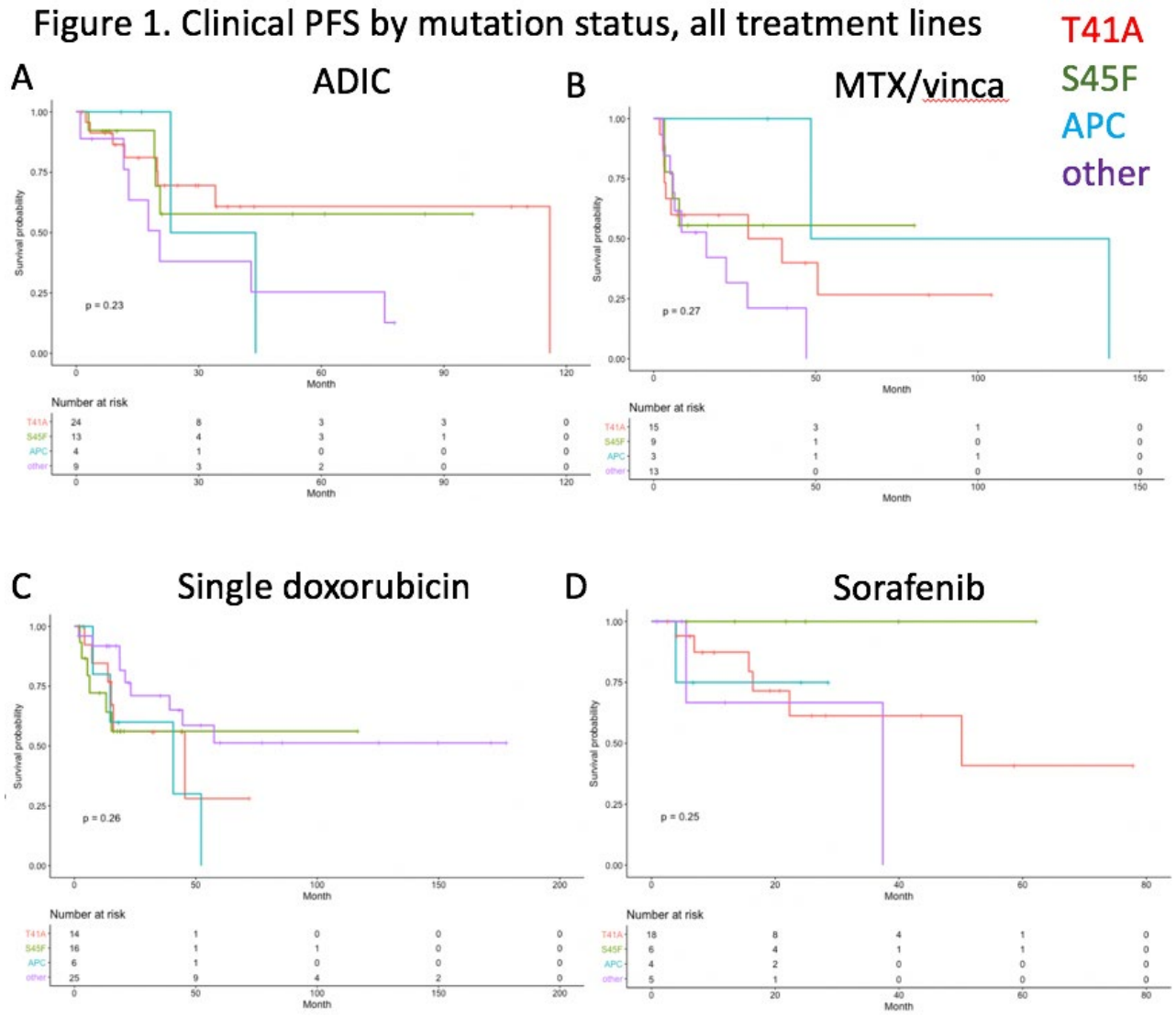
Table 1. Univariable and multivariable Cox proportional hazard model analysis

Variable		1st Line Clinical PFS			2nd Line Clinical PFS		
		N (%)	Hazard Ratio (univariable) 95% CI, P value	Hazard Ratio (multivariable) 95% CI, P value	N (%)	Hazard Ratio (univariable) 95% CI, P value	Hazard Ratio (multivariable) 95% CI, P value
Mutation	T41A	45 (37)	-	-	45 (41)	-	-
	S45F	36 (30)	1.14 (0.61-2.13, p=0.681)	0.93 (0.45-1.90, p=0.833)	28 (26)	1.73 (0.92-3.25, p=0.090)	2.02 (0.88-4.61, p=0.096)
	APC	10 (8)	1.75 (0.75-4.10, p=0.195)	4.93 (1.21-20.01, p=0.026)	7 (6)	2.09 (0.78-5.57, p=0.140)	4.86 (0.68-34.77, p=0.116)
	Other [1]	31 (25)	0.89 (0.49-1.61, p=0.703)	1.53 (0.60-3.91, p=0.376)	29 (27)	1.21 (0.62-2.39, p=0.574)	0.59 (0.19-1.83, p=0.363)
Treatment	Surgery [2]	66 (35)	-	-	31 (21)	-	-
	ADIC	20 (11)	0.29 (0.12-0.72, p=0.008)	0.32 (0.12-0.85, p=0.023)	18 (12)	0.38 (0.14-1.00, p=0.049)	0.24 (0.06-0.96, p=0.044)
	Single agent doxorubicin [3]	34 (18)	0.29 (0.15-0.57, p<0.001)	0.39 (0.16-0.99, p=0.047)	22 (15)	0.49 (0.22-1.09, p=0.080)	0.36 (0.09-1.40, p=0.139)
	Sorafenib	10 (5)	0.28 (0.07-1.13, p=0.074)	0.19 (0.02-1.46, p=0.110)	13 (9)	0.25 (0.06-1.07, p=0.063)	0.13 (0.01-1.32, p=0.084)
	MTX/vinca alkaloids [4]	23 (12)	0.35 (0.17-0.71, p=0.004)	0.39 (0.11-1.41, p=0.149)	15 (10)	1.08 (0.50-2.35, p=0.844)	1.19 (0.44-3.19, p=0.731)
	Other [5]	36 (19)	0.60 (0.36-0.99, p=0.045)	1.65 (0.77-3.52, p=0.195)	46 (32)	0.90 (0.50-1.61, p=0.723)	1.77 (0.71-4.39, p=0.217)
Sex	Female	125 (66)	-	-	99 (68)	-	-
	Male	64 (34)	0.75 (0.49-1.15, p=0.187)	0.68 (0.35-1.33, p=0.263)	46 (32)	0.90 (0.54-1.51, p=0.693)	0.73 (0.32-1.68, p=0.462)
Race	Caucasian	115 (68)	-	-	92 (70)	-	-
	Hispanic/ Latino	23 (14)	0.91 (0.48-1.73, p=0.777)	1.59 (0.66-3.81, p=0.303)	17 (13)	1.59 (0.77-3.29, p=0.210)	2.99 (0.98-9.07, p=0.053)
	Afri-can-Ameri-can/Black	15 (9)	1.08 (0.54-2.18, p=0.825)	1.16 (0.51-2.63, p=0.726)	11 (8)	1.24 (0.53-2.91, p=0.626)	0.75 (0.21-2.66, p=0.650)
	Asian	8 (5)	0.77 (0.24-2.46, p=0.660)	0.72 (0.17-3.12, p=0.659)	4 (3)	NA	NA
	Other/Un-known	7 (4)	0.94 (0.34-2.60, p=0.909)	0.55 (0.05-5.87, p=0.619)	7 (5)	3.05 (1.19-7.86, p=0.021)	3.16 (0.43-23.37, p=0.260)
Age (Years)	Mean (SD)	36.9 (14.9)	0.99 (0.97-1.00, p=0.098)	0.98 (0.95-1.00, p=0.047)	35.3 (13.8)	0.98 (0.97-1.00, p=0.065)	0.97 (0.95-1.00, p=0.045)
Location	Mesenteric/ Abdominal [6]	67 (35)	-	-	53 (37)	-	-
	Extremity/ Trunk	94 (50)	0.86 (0.56-1.32, p=0.500)	1.02 (0.53-1.97, p=0.956)	75 (52)	1.52 (0.88-2.63, p=0.129)	1.09 (0.43-2.73, p=0.859)
	Other [7]	28 (15)	1.12 (0.63-1.98, p=0.708)	0.95 (0.44-2.05, p=0.897)	17 (12)	1.83 (0.85-3.94, p=0.123)	0.28 (0.08-0.95, p=0.042)

FAP History	No	141 (79)	-	-	113 (80)	-	-
	Yes	37 (21)	1.09 (0.70-1.69, p=0.711)	0.34 (0.12-1.03, p=0.056)	28 (20)	1.50 (0.87-2.60, p=0.144)	1.03 (0.26-4.16, p=0.963)
Time to 2nd Tx (months)	Mean (SD)	NA	NA	NA	15.6 (19.9)	1.00 (0.99-1.01, p=0.988)	1.02 (1.00-1.05, p=0.050)

1. Other reflects S45P (n=5), samples testing negative for T41A, S45F, and S45P mutations (MDACC/MSMC) or negative for CTNNB1 and APC mutations (UM, DFCI), or other identified mutations.
2. Surgery with or without adjuvant therapies.
3. Single agent doxorubicin or liposomal doxorubicin.
4. Methotrexate and/or vinblastine, vinorelbine, or other vinca alkaloids.
5. Other is 60% tamoxifen with or without anti-inflammatories, other TKIs including imatinib, and other chemotherapy regimens.
6. Includes retroperitoneal and pelvic lesions.
7. Includes other locations or multifocal tumors.
   Abbreviations: PFS (progression-free survival), 95% CI (confidence interval), ADIC (doxorubicin/dacarbazine), SD (standard deviation)

Figure 1. Clinical progression-free survival was determined for systemic chemotherapy regimens regardless of line of therapy and compared by mutation status.



Paper #38 3461713

PHASE 1 DOSE-ESCALATION STUDY OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF DCC-3014 IN ADVANCED SOLID TUMORS AND TENOSYNOVIAL GIANT CELL TUMOR (TGCT)

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Objective: DCC-3014 is a small molecule, oral, investigational kinase switch control inhibitor that is highly selective for colony-stimulating factor 1 receptor (CSF1R). DCC-3014 exhibits nanomolar potency for CSF1R and >100-fold selectivity vs closely related kinases (KIT, PDGFRα, PDGFRβ and FLT3). TGCT is a rare, locally aggressive neoplasm which is caused by a translocation in the CSF1 gene that results in overexpression of CSF1. Most TGCTs consist of CSF1R signaling dependent inflammatory macrophage infiltrates that migrate and proliferate in the joints and surrounding tissue, which can lead to severe morbidity. Anti-CSF1R therapies have shown clinical activity in TGCT. Pexidartinib, a broad-spectrum kinase inhibitor, is the only FDA-approved therapy for patients (pts) with symptomatic TGCT not amenable to surgery but is associated with potential hepatotoxicity. The greater selectivity and initial observed antitumor activity of DCC-3014 in this ongoing study warrants its further evaluation in pts with TGCT. Here we report an update on the safety and efficacy data of a phase 1 study of DCC-3014 in solid tumors and inoperable TGCT.

Methods: This is a dose-escalation and dose-expansion, first-in-human study of DCC-3014 in pts with solid tumors and inoperable TGCT utilizing a 3+3 design (NCT03069469). The primary objectives of dose escalation are to assess safety and tolerability, characterize pharmacokinetics, and to determine maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Preliminary evidence of antitumor activity and pharmacodynamics (PD) are exploratory endpoints in dose escalation. DCC-3014 is given orally in a 28-day cycle.

Results: As of May 15, 2020, dose escalation is ongoing with enrollment of 47 pts across 9 cohorts (Table). Data from cohorts 1–8, including 37 malignant solid tumor and 9 TGCT pts, are presented. The median age of pts was 59 years and the median duration on treatment was 1.8 months. Most commonly reported treatment-emergent adverse events (AEs) (≥ 20%, mostly grade 1/2) in the 46 pts were constipation (33%), periorbital edema (30%), vomiting (30%), AST increased (28%), fatigue (28%), CPK increased (26%), diarrhea (26%), nausea (26%), abdominal pain (20%), decreased appetite (20%), dyspnea (20%) and lipase increased (20%). Serious AEs (SAEs) were seen in 19 pts; none were related to DCC-3014. One dose-limiting toxicity of asymptomatic Grade 3 AST elevation was reported in Cohort 8, leading to a delay in treatment and subsequent discontinuation from study. Asymptomatic CPK and AST elevations observed were consistent with CSF1R inhibition and decreased clearance of these enzymes by liver macrophages. No bilirubin elevations and/or other laboratory abnormalities typically associated with liver damage have been observed. Exposure was approximately dose proportional, with induction of CSF1 and reduction in circulating levels of non-classical monocytes seen across cohorts. Seven of nine TGCT pts are still on study as of the data cutoff (one discontinuation was due to withdrawal due to relocation out of the country). Two TGCT pts who have received ≥6 months of treatment both have an ongoing partial response in cycle 11 and cycle 17, respectively. Per investigator reports, both pts experienced early and sustained improvement in pain, swelling, and function. Efficacy data for the recently enrolled TGCT pts will be presented at the congress.

Conclusion: DCC-3014 in this ongoing study was generally well tolerated in pts with solid tumors and in those with inoperable TGCT, with most AEs grade 1 or 2 in severity. DCC-3014 demonstrated approximately dose-proportional exposure and PD effects. Dose-escalation evaluation is still ongoing to determine the RP2D and the MTD has not been reached. Updated antitumor activity in 2 TGCT pts on treatment for ≥6 months shows durable, deepening response by RECIST. Overall, these results support the ongoing evaluation of DCC-3014 in pts with inoperable TGCT.

Dose cohorts in Part 1 dose escalation

	Loading Doses	Dose
Cohort 1	None	10 mg QD
Cohort 2	10 mg QD x 5 days	10 mg twice a week
Cohort 3	20 mg QD x 5 days	20 mg once a week
Cohort 4	20 mg QD x 5 days	20 mg twice a week
Cohort 5	30 mg QD x 5 days	30 mg twice a week
Cohort 6	40 mg QD x 5 days	40 mg twice a week
Cohort 7	50 mg QD x 3 days	20 mg QD
Cohort 8	30 mg QD x 3 days	10 mg QD
Cohort 9	20 mg QD x 3 days	6 mg QD

QD, once daily.

Poster #001 3412554
DIFFICULTY OF DISTINGUISHING ARTERIAL INTIMAL SARCOMA FROM CHRONIC PULMONARY EMBOLISM THROUGH DIFFERENTIAL DIAGNOSIS
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Poster #002 3412790
APATINIB FOR TREATMENT OF INOPERABLE METASTATIC OR LOCALLY ADVANCED CHONDROSARCOMA: WHAT CAN WE LEARN ABOUT THE BIOLOGICAL BEHAVIOR OF CHONDROSARCOMA FROM A MULTICENTER STUDY
Lu Xie[1], *Jie Xu*[1], *Jin Gu*[2], *Zhe Lv*[3], *Xiaodong Tang*[1], *Wei Guo*[1]
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Poster #003 3412794
DYNAMIC CHANGES IN QUALITY OF LIFE AND Q-TWIST ANALYSIS FOR EWING SARCOMA PATIENTS FOLLOWING ANLOTINIB AND IRINOTECAN, A COMBINATION OF PHASE 1B AND 2 TRIAL
Lu Xie[1], *Jie Xu*[1], *Wei Guo*[1], *Xin Sun*[1], *Xiaodong Tang*[1]
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Poster #004 3412832
THE CLINICAL IMPLICATIONS OF TUMOR MUTATIONAL BURDEN IN OSTEOSARCOMA
Lu Xie[1], *Yu-Fei Yang*[2], *Wei Guo*[1], *Dongxue Che*[2], *Jie Xu*[1], *Xin Sun*[1], *Kuisheng Liu*[1], *Xiaodong Tang*[1]
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Poster #005 3413225
EXTRASKELETAL MYXOID CHONDROSARCOMA: A HIGH INCIDENCE OF METASTATIC DISEASE TO LYMPH NODES
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Poster #006 3420516
CLINICAL EXPERIENCE OF 6 CASES OF MYXOID PLEOMORPHIC LIPOSARCOMA
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Poster #007 3425027

VERSICAN AND EXTRACELLULAR MATRIX REMODELING PROMOTE CIRCULATING OSTEOSARCOMA CELL EXTRAVASATION AND METASTATIC SEEDING

Mark M. Cullen[1], *Tyler A. Allen*[2], *Lan Nguyen*[3], *Hiroyuki Mochizuk*[6], *Paige Nemec*[6], *Etienne M. Flamant*[1], *Sarah Hoskinson*[4], *Beatrice Thomas*[2], *Suzanne B. DeWitt*[4], *Kathryn E. Ware*[2], *Luke Borst*[6], *Ke Cheng*[6], *William C. Eward*[5], *Jason A. Somarelli*[2]

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Poster #008 3427115

THE ANATOMIC DISTRIBUTION OF OSTEOSARCOMA

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Poster #009 3428769

PROGNOSIS OF PATIENTS WITH METASTATIC SOFT TISSUE SARCOMA: ADVANCES IN RECENT YEARS

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Poster #010 3434418

RECURRENT MULTIFOCAL PLEOMORPHIC SARCOMA OF THE SCALP RESPONDING TO PEMBROLIZUMAB

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Poster #011 3434659

PROGNOSTIC FACTORS OF HIGH-GRADE OSTEOSARCOMA: ANALYSIS OF 20 YEARS DATA AT A SINGLE CENTER IN JAPAN

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Poster #012 3436390

CHARACTERISTICS AND OUTCOMES OF LOCALLY RECURRENT RETROPERITONEAL SARCOMA AFTER FIRST RELAPSE IN A SINGLE TERTIARY ASIAN CENTRE AND APPLICABILITY OF THE SARCULATOR

Hui Jun Lim[2], *Ru Xin Wong*[1], *Yen Sin Koh*[1], *Zhirui Shaun Ho*[1], *Chin-Ann Johnny Ong*[2], *Farid Bin Harunal Rashid Mohamad*[3], *Ching Ching Melissa Teo*[2]

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Poster #013 3436645

CURRICULUM-BASED ONLINE CME IMPROVES PHYSICIAN KNOWLEDGE OF EPITHELIOID SARCOMA

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Poster #014 3436999

ASSOCIATION BETWEEN OCCUPATIONAL EXPOSURES AND SARCOMA INCIDENCE AND MORTALITY: SYSTEMATIC REVIEW AND META-ANALYSIS

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Poster #015 3437318

PELVIC SOFT TISSUE SARCOMAS: AN INTERNATIONAL RETROSPECTIVE STUDY FROM THE TRANS-ATLANTIC AUSTRALASIAN RETROPERITONEAL SARCOMA WORKING GROUP (TARPSWG)

Marco Fiore[1], *Catherine Sarre-Lazcano*[1], *Sinziana Dumitra*[2], *Charles Honoré*[3], *Paul Sargos*[4], *Giovanni Grignani*[5], *Shintaro Iwata*[6], *Carolyn Nessim*[7], *Marko Novak*[8], *Dmitri Tzanis*[9], *David E. Gyorki*[10], *Piotr Rutkowski*[11], *Antoine Bouchard-Fortier*[12], *Kenneth Cardona*[13], *Sergio D. Quildrian*[14], *Dorian Y. Garcia-Ortega*[17], *Winan J. van Houdt*[15], *Sergio Valeri*[16], *Carlo Abatini*[1], *Mario Terlizzi*[4], *Francesco Tolomeo*[5], *Michelle J. Wilkinson*[10], *Jecek Skoczylas*[11], *Sandro Pasquali*[1], *Alessandro Gronchi*[1]
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Poster #016 3437396

OSTEOSARCOMA ORGANOIDS DEMONSTRATE FUNCTIONAL AND THERAPEUTIC HETEROGENEITY DEPENDING UPON GEOGRAPHIC SITE OF ORIGIN WITHIN THE TUMOR

Etienne M. Flamant[1], *Mark M. Cullen*[1], *Sarah Hoskinson*[2], *Beatrice Thomas*[3], *Sehwa Oh*[3], *Gabrielle Rupprecht*[3], *Joanne Tuohy*[4], *David S. Hsu*[3], *William C. Eward*[2], *Jason A. Somarelli*[3]
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Poster #017 3437413

RADIOLOGICAL ANALYSIS OF TUMOR RESPONSE TO AN EFFECTIVE TYROSINE KINASE INHIBITOR (TKI), PEXIDARTINIB, IN TENOSYNOVIAL GIANT CELL TUMORS (TGCT) FROM THE PHASE 3 ENLIVEN STUDY

Charles Peterfy[1], *William D. Tap*[2], *John H. Healey*[2], *Andrew J. Wagner*[3], *Souhil Zaim*[4], *Hans Bloem*[5], *Qiang Wang*[6], *Dale Shuster*[6], *Yan Chen*[1], *Michiel van de Sande*[5]
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Poster #018 3437421

A NOVEL PRE-OPERATIVE RISK SCORE TO GUIDE PATIENT SELECTION FOR RESECTION OF SOFT TISSUE SARCOMA LUNG METASTASES: AN ANALYSIS FROM THE UNITED STATES SARCOMA COLLABORATIVE

Rachel Lee[1], *Cecilia Ethun*[1], *Adriana Gamboa*[1], *Michael Turgeon*[1], *Thuy Tran*[2], *George Poultsides*[2], *Valerie Grignol*[3], *J H. Howard*[3], *Meena Bedi*[4], *Harveshp Mogal*[5], *Callisia Clarke*[5], *Jennifer Tseng*[6], *Kevin Roggin*[6], *Konstantinos Chouliaras*[7], *Konstantinos Votanopoulos*[7], *Bradley Krasnick*[8], *Ryan Fields*[8], *Shervin Oskouei*[1], *David Monson*[1], *Nickolas Reimer*[1], *Shishir Maithel*[1], *Allan Pickens*[9], *Kenneth Cardona*[1]

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Poster #019 3437427

THE ACCURACY OF A NOVEL SONOGRAPHIC SCANNING AND REPORTING PROTOCOL TO SURVEY FOR SOFT TISSUE SARCOMA LOCAL RECURRENCE: RESULTS OF A PROSPECTIVE PILOT STUDY

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Poster #020 3437455

HISTOLOGICAL VARIATION AFTER PRE-OPERATIVE HYPOFRACTIONATED VERSUS STANDARD FRACTION RADIOTHERAPY IN SOFT TISSUE SARCOMAS

Casey Hollawell[1], *Yulan Gong*[2], *Lori Rink*[2], *Elizabeth Handorf*[2], *Michael Shu*[1], *Margaret von Mehren*[2], *Jeffrey Farma*[2], *Stephanie Greco*[2], *John Abraham*[3], *Josh Meyer*[2], *Krisha J. Howell*[2]

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Poster #021 3437674

STRIVE-01: PHASE I STUDY OF EGFR806 CAR T CELL IMMUNOTHERAPY FOR RECURRENT/REFRACTORY SOLID TUMORS IN CHILDREN AND YOUNG ADULTS

Catherine M. Albert[1], *Navin R. Pinto*[1], *Adam J. Johnson*[1], *Ashley L. Wilson*[1], *Stephanie Mgebroff*[1], *Christopher Brown*[1], *Catherine Lindgren*[1], *Erin Rudzinski*[2], *Bonnie L. Cole*[2], *Nicholas A. Vitanza*[1], *Juliane Gust*[3], *Michael C. Jensen*[1], *Julie Park*[1]

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Poster #022 3437802

NICLOSAMIDE STEARATE PRODRUG THERAPEUTIC (NSPT) ENHANCES MITOCHONDRIAL PROTON LEAK AND INDUCES POTENT CYTOTOXICITY IN OSTEOSARCOMAS

Mark M. Cullen[1], *Etienne M. Flamant*[1], *Philip H. Khoury*[2], *Hailey E. Brighton*[6], *David L. Kerr*[7], *Gireesh B. Reddy*[8], *Sarah Hoskinson*[6], *Harrison R. Ferlauto*[1], *Suzanne B. DeWitt*[6], *Kathryn E. Ware*[6], *Beatrice Thomas*[6], *Julia D. Visgauss*[4], *Brian E. Brigman*[4], *Jason A. Somarelli*[3], *David Needham*[5], *William C. Eward*[4]

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Poster #023 3438818

MAGNETIC RESONANCE GUIDED HIGH INTENSITY FOCUSED ULTRASOUND IN COMBINATION WITH THERMOSENSITIVE LIPOSOMAL DOXORUBICIN AS A NOVEL TREATMENT FOR RHABDOMYOSARCOMA

Claire Wunker[1], *Ben Keunen*[3], *Karolina Piorkowska*[3], *Warren Foltz*[4], *Maximilian Regenold*[5], *Yael Babichev*[1], *Michael Dunne*[5], *Maryam Siddiqui*[6], *Samuel Pichardo*[6], *Christine Allen*[5], *Adam Waspe*[3], *Rebecca Gladdy*[1], *Justin T. Gerstle*[2]

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Poster #024 3439734

SOFT TISSUE SARCOMA: IS THERE A SURVIVAL GAP BETWEEN MIDDLE-AGED AND ELDERLY PATIENTS?

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Poster #025 3439834

MACHINE LEARNING TOOL SUCESSFULLY CLASSIFIES TREATMENT RESPONSE IN HIGH-GRADE OSTEOSARCOMA

Patrick Leavey[1], *Ka Yaw Teo*[2], *Karin Claussen*[1], *Kevin Cederberg*[3], *Rami Hallac*[4], *Anita Sengupta*[5], *Alexandra Callan*[6], *Ovidiu Daescu*[2]

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Poster #026 3440865

OUTCOME OF COMBINING RESECTION OF SARCOMA WITH INVOLVED BOWELS IN PATIENTS WITH PRIMARY RETROPERITONEAL LIPOSARCOMA

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Poster #027 3441221

A PHASE 1, MULTICENTER, OPEN-LABEL, FIRST-IN-HUMAN STUDY OF DS-6157A IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR

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Poster #028 3441532

DUAL-ENERGY CT AS A QUANTITATIVE RESPONSE PARAMETER IN PATIENTS WITH GIST UNDERGOING TARGETED THERAPY – A PROSPECTIVE MULTI-CENTER TRIAL

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Poster #029 3441865

PROGNOSES OF SUPERFICIAL SOFT TISSUE SARCOMA: THE IMPORTANCE OF FASCIA-TUMOR RELATIONSHIP ON MRI

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Poster #030 3442000

OUTCOME OF CLINICAL GENETIC TESTING IN PATIENTS WITH SARCOMA

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Poster #031 3442052

VARIANCE BETWEEN EXPERTS AND COMMUNITY PRACTITIONERS IN TREATING SOFT TISSUE SARCOMAS: ANALYSIS OF AN ONLINE DECISION SUPPORT TOOL

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Poster #032 3442782

ANTI-TUMOR EFFECT OF LAT1 INHIBITOR ON CLEAR CELL SARCOMA CELL LINE

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Poster #033 3443018

OPPORTUNISTIC MUSCLE MEASUREMENTS ON STAGING CHEST CT FOR EXTREMITY AND TRUNCAL SOFT TISSUE SARCOMA ARE ASSOCIATED WITH SURVIVAL

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Poster #034 3443510

IS SURGICAL RESECTION OF THE PRIMARY SITE ASSOCIATED WITH AN IMPROVED OVERALL SURVIVAL FOR PRIMARY MALIGNANT BONE TUMORS WITH METASTATIC DISEASE AT PRESENTATION?

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Poster #035 3443839

CRYOABLATION: AN EFFECTIVE AND SAFE OPTION IN THE TREATMENT ALGORITHM OF EXTRA-ABDOMINAL DESMOID TUMORS?

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Poster #036 3445136

DEVELOPMENT OF A NOVEL ORGANS-ON-A-CHIP MODEL THAT ENABLES PREDICTIVE AND CLINICALLY RELEVANT DRUG SCREENING TO DETERMINE EWING SARCOMA ANTI-TUMOR EFFICACY AND CARDIAC SAFETY

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Poster #037 3446023

THE NITRASARC TRIAL- A NON-RANDOMIZED, OPEN-LABEL PHASE II TRIAL EVALUATING EFFICACY AND FEASIBILITY OF COMBINED TREATMENT WITH TRABECTEDIN AND NIVOLUMAB IN PATIENTS WITH METASTATIC OR INOPERABLE SOFT TISSUE SARCOMAS AFTER FAILURE OF AN ANTHRACYCLINE-CONTAINING REGIMEN: INTERIM SAFETY ANALYSIS

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Poster #038 3446269

TOPP: TENOSYNOVIAL GIANT CELL TUMOR OBSERVATIONAL PLATFORM PROJECT—PATIENT-REPORTED SYMPTOMS AND QUALITY OF LIFE (QOL) FROM A EUROPEAN AND US PROSPECTIVE REGISTRY

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Poster #039 3446499

THE DIFFUSE-TYPE TGCT PATIENT JOURNEY: A PROSPECTIVE MULTICENTER STUDY

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Poster #040 3448478

TREATMENT OUTCOME OF SUPERFICIAL LEIOMYOSARCOMA

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Poster #041 3449895

MOLECULAR ANALYSIS OF ARCHIVAL CLEAR CELL SARCOMA TISSUE SAMPLES FROM EORTC TRIAL 90101 "CREATE" AND CORRELATION WITH RESPONSE TO CRIZOTINIB

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Poster #042 3450727

OPTICAL SENSOR FOR RAPID BACTERIAL DETECTION AND DIAGNOSIS OF IMPLANT ASSOCIATED INFECTIONS IN CANCER PATIENTS

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Poster #043 3451306

USE OF FDG POSITRON EMISSION TOMOGRAPHY TO PREDICT CHEMOTHERAPY RESPONSE AND OUTCOMES IN PEDIATRIC BONE SARCOMAS

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Poster #044 3452161

THE AGE-RELATED IMPACT OF SURVIVING SARCOMA ON HEALTH-RELATED QUALITY OF LIFE: DATA FROM THE DUTCH SURVSARC STUDY

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Poster #045 3452220

PROMISING ACTIVITY OF AN ENZYME-ACTIVATED DOXORUBICIN PRODRUG IN A PANEL OF PATIENT-DERIVED XENOGRAFT MODELS OF SOFT TISSUE SARCOMA

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Poster #046 3452295

BACTERIOPHAGE COCKTAIL TO IMPROVE TREATMENT OF IMPLANT-ASSOCIATED BACTERIAL INFECTIONS IN CANCER PATIENTS

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Poster #047 3452402

SYSTEMIC INFLAMMATION RESPONSE INDEX (SIRI) AS A PREDICTIVE FACTOR FOR OVERALL SURVIVAL IN ADVANCED SOFT TISSUE SARCOMA TREATED WITH ERIBULIN

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Poster #048 3452426

STING ACTIVATION AS AN IMMUNOTHERAPEUTIC STRATEGY FOR SOFT TISSUE SARCOMA

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Poster #049 3452445

REGORAFENIB FOR PROGRESSIVE RELAPSED METASTATIC OSTEOSARCOMA IN AN ADOLESCENT

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Poster #050 3452498

OPTIMIZED PATIENT-DERIVED 3D SARCOMA MODEL – ROBUST SYSTEM FOR SARCOMA RESEARCH

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Poster #051 3452630

SAFE CLINICAL COMPATIBILITY OF A NON-INVASIVE EXTENDIBLE ELECTROMAGNETIC PROSTHESIS WITH AN IN SITU VENTRICULAR ASSIST DEVICE

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Poster #052 3452817

SELINEXOR, A FIRST IN CLASS NUCLEAR EXPORT INHIBITOR, FOR THE TREATMENT OF ADVANCED MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

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Poster #053 3452862

UNRAVELLING THE HETEROGENEITY OF SARCOMA PATIENTS' HEALTH-RELATED QUALITY OF LIFE: IMPACT OF PRIMARY SARCOMA LOCATION

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Poster #054 3453418

A RANDOMIZED, OPEN-LABEL PHASE 1/2 STUDY OF RAMUCIRUMAB IN COMBINATION WITH CHEMOTHERAPY IN PEDIATRIC PATIENTS AND YOUNG ADULTS WITH RELAPSED, RECURRENT, OR REFRACTORY DESMOPLASTIC SMALL ROUND CELL TUMOR OR SYNOVIAL SARCOMA

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Poster #055 3454087

A RETROSPECTIVE COHORT STUDY ON THE IMPACT OF REGIONAL ANESTHESIA IN SARCOMA RESECTION SURGERY

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Poster #056 3454710

CLINICAL AND MOLECULAR CHARACTERISTICS OF A CASE SERIES OF GIST WITH EXTRA-ABDOMINAL METASTASES

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Poster #057 3454819

CIRCULATING TUMOUR DNA: A POTENTIAL TOOL FOR SARCOMA MANAGEMENT

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Poster #058 3455149

(GIST) PATIENTS WITH KNOWN MUTATION TRANSITION TO SUBSEQUENT TREATMENTS AT A HIGHER RATE AND HAVE SUPERIOR SURVIVAL COMPARED TO PATIENTS WITHOUT KNOWN MUTATION: RESULTS FROM THE LIFERAFT GROUP (LRG) GIST REGISTRY

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Poster #059 3455363

SUPERFICIAL FIBROMATOSIS LESION SIZE CORRELATES WITH MRI T2 MAPPING AND IMAGE TEXTURE FEATURES

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Poster #060 3455537

TARGETING THE CMG HELICASE AS A "NEVER" MUTATION TO REDUCE CELLULAR FITNESS IN OSTEOSARCOMA CELLS

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Poster #061 3455574

CHARACTERIZING GROWTH UNDER SELECTION FOR OSTEOSARCOMA HETEROGENEITY MODEL

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Poster #062 3455662

EXPLORATION OF IMAGING BIOMARKERS FOR METABOLICALLY-TARGETED OSTEOSARCOMA THERAPY

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Poster #063 3456222

FACTORS AFFECTING GENETIC CONSULTATION IN ADOLESCENT AND YOUNG ADULT PATIENTS WITH SARCOMA

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Poster #064 3457423

RETROSPECTIVE ANALYSIS OF 18 YEARS OF TREATMENT OF MYXOFIBROSARCOMAS IN THE NETHERLANDS

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Poster #065 3457767

OUTCOMES OF PATIENTS WITH SARCOMA AND COVID-19: A SINGLE INSTITUTION EXPERIENCE

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Poster #066 3457998

DECISIONAL CONTROL PREFERENCES IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMAS STARTING 1ST LINE PALLIATIVE CHEMOTHERAPY: RESULTS FROM THE HOLISTIC STUDY

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Poster #067 3458044

IMRIS: A PHASE II STUDY OF INTENSITY MODULATED RADIOTHERAPY (IMRT) IN EXTREMITY SOFT TISSUE SARCOMA (STS)

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Poster #068 3458250

GENETIC MODELS REVEAL THAT THE NOVEL *VGLL2-NCOA2* FUSION ONCOGENE LEVERAGES EMBRYONIC PROGRAMS FOR SARCOMAGENESIS

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Poster #069 3458308

CONTEMPORARY OUTCOMES AND SECONDARY AMPUTATION AFTER LOCAL RECURRENCE IN PATIENTS AFFECTED BY EXTREMITY SOFT TISSUE SARCOMA TREATED WITH LIMB-SPARING SURGERY AT A REFERENCE INSTITUTION

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Poster #070 3458516

HARNESSING THE ELECTRONIC MEDICAL RECORD TO IMPROVE THE EVALUATION OF SOFT TISSUE MASSES IN THE PRIMARY CARE SETTING: A PILOT STUDY ON THE IMPACT OF A BEST PRACTICE ALERT

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Poster #071 3458545

TUMOR RESPONSE TO WINDOW THERAPY WITH TEMSIROLIMUS, IRINOTECAN, AND TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED HIGH-RISK EWING SARCOMA; A PHASE II SINGLE INSTITUTION STUDY

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Poster #072 3458703

RETROSPECTIVE ANALYSIS OF THE CLINICAL PRESENTATION, TREATMENT AND OUTCOME OF ANGIOSARCOMA IN A SARCOMA REFERRAL CENTER

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Poster #073 3458722

POTENTIAL MOLECULAR BIOMARKERS OF RESPONSE TO ERIBULIN IN PATIENTS WITH LEIOMYOSARCOMA

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Poster #074 3458723

GENETIC PROFILE OF GASTROINTESTINAL STROMAL TUMORS (GIST) TREATED IN EORTC 1317 "CABOGIST" PHASE 2 TRIAL

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Poster #075 3458771

LONG-TERM OUTCOME OF PATIENTS WITH NONMETASTATIC BONE OSTEOSARCOMA: A CONDITIONAL SURVIVAL ANALYSIS

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Poster #076 3458918

EVALUATION OF PROGNOSTIC NOMOGRAMS FOR OUTCOMES AFTER RESECTION OF PRIMARY RETROPERITONEAL SARCOMA

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Poster #077 3459835

DEVELOPMENT OF RHABDOMYOSARCOMA SPECIFIC SEQUENCING ASSAY

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Poster #078 3459966

THE PROGNOSTIC IMPORTANCE OF PATHOLOGIC FRACTURE IN LIMB SALVAGE SURGERY FOR OSTEOSARCOMA: A SINGLE-INSTITUTION REVIEW OF 304 PATIENTS

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Poster #079 3459977

SARCOMA IN YOUNG AGE – AN OVERVIEW OF CLINICAL, PATHOLOGICAL AND MOLECULAR FINDINGS IN A LARGE SINGLE CENTER COHORT

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Poster #080 3460220

THE UTILITY OF FDG PET-CT SCAN IN OFF-TREATMENT SURVEILLANCE OF PEDIATRIC BONE TUMORS

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Poster #081 3460229

NEUTROPHIL-LYMPHOCYTE AND PLATELET-LYMPHOCYTE RATIOS AS ROBUST PROGNOSTIC MARKERS IN SARCOMAS - A POPULATION-BASED ANAYLSIS OF 3746 SARCOMA PATIENTS FROM HONG KONG

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Poster #082 3460268

AGE RELATED DIFFERENCES OF ONCOLOGICAL OUTCOMES IN PRIMARY EXTREMITY SOFT TISSUE SARCOMA: A MULTISTATE MODEL INCLUDING 6260 PATIENTS

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Poster #083 3460427

ANALYSIS OF TUMOR INFILTRATING NK AND T CELLS HIGHLIGHTS IL-15 STIMULATION AND TIGIT BLOCKADE AS A COMBINATION IMMUNOTHERAPY STRATEGY FOR SOFT TISSUE SARCOMAS

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Poster #084 3460650

MANAGEMENT AND OUTCOMES OF CIC-REARRANGED SARCOMA; AN AUSTRALIAN MULTI-CENTRE REVIEW

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Poster #085 3460865

IDENTIFICATION OF NOVEL THERAPEUTIC TARGETS FOR METASTATIC OSTEOSARCOMA

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Poster #086 3460952

EVALUATION OF CIRCULATING TUMOR CELLS IN RECURRENT OSTEOSARCOMA PATIENTS TREATED ON A PHASE II TRIAL OF GEMCITABINE AND NAB-PACLITAXEL: A REPORT FROM THE NATIONAL PEDIATRIC CANCER FOUNDATION

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Poster #087 3461000

UBIQUITIN-LIGASE ATROGIN MEDIATES ADAPTATION TO KIT TARGETED INHIBITION IN GASTROINTESTINAL STROMAL TUMOR

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Poster #088 3461083

BONE METASTASIS OF GASTROINTESTINAL STROMAL TUMOR: CASE REPORT AND REVIEW OF THE LITERATURE

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Poster #089 3461140

FIVE-YEAR SURVIVAL OF A PATIENT WITH DEDIFFERENTIATED CHONDROSARCOMA TREATED WITH CHEMOTHERAPY AND JOINT SPARING SURGERY

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Poster #090 3461203

IMPACT OF IMMUNOTHERAPY AND TARGETED THERAPY ON TUMOR GROWTH RATE IN SARCOMA

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Poster #091 3461252

PRIMARY SITE SURGERY IS ASSOCIATED WITH IMPROVED SURVIVAL IN METASTATIC SOFT TISSUE SARCOMA OF THE EXTREMITY

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Poster #092 3461276

CHARACTERIZATION OF TUMOR INFILTRATING IMMUNE CELLS FROM ADULT SOFT TISSUE SARCOMAS

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Poster #093 3461301

IMPACT OF NEOADJUVANT CHEMOTHERAPY FOR RETROPERITONEAL SARCOMAS: A PROPENSITY BASED ANALYSIS OF A RETROSPECTIVE INTERNATIONAL, MULTICENTER COHORT

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Poster #094 3461333

SURGICAL MANAGEMENT OF PRIMARY LESION OF SOFT TISSUE SARCOMA MAY IMPROVE OVERALL SURVIVAL OF PATIENTS WITH INITIAL METASTASIS

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Poster #095 3461335

PATIENT-SPECIFIC CUTTING GUIDES AND 3D-PRINTED TECHNOLOGY FOR PELVIC AND SACRAL TUMOR RESECTION AND COMPLEX ALLOGRAFT RECONSTRUCTION: OUR EXPERIENCE IN THE RESECTION OF PELVIC AND SPINAL SARCOMA OF BONE

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Poster #096 3461337

NON-RANDOM ASSOCIATION OF BREAST IMPLANT SURGERY AND DESMOID TUMOR FORMATION

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Poster #097 3461438

A PHASE 1B/3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF TAZEMETOSTAT PLUS DOXORUBICIN AS FRONTLINE THERAPY FOR PATIENTS WITH ADVANCED EPITHELIOID SARCOMA

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Poster #098 3461452

OUTCOMES OF EWING SARCOMA/ EWING'S-LIKE SARCOMA (ES) IN PATIENTS AGED OVER 25

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Poster #099 3461465

GRADE OF PRIMARY CUTANEOUS LEIOMYOSARCOMA DICTATES CLINICAL OUTCOME RISK

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Poster #100 3461487

OXYGEN TENSION AND MACROPHAGES MEDIATE PROLIFERATION OF OSTEOSARCOMA CELLS IN 3-DIMENSIONAL CULTURE

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Poster #101 3461493

PATIENT-SPECIFIC CUTTING GUIDES AND 3D-PRINTED TECHNOLOGY FOR INTERCALARY LONG BONE RESECTION AND ALLOGRAFT RECONSTRUCTION: OUR EXPERIENCE IN THE RESECTION OF EXTREMITY SARCOMA OF BONE

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Poster #102 3461507

SHORTCOMINGS OF FUNCTIONAL IMAGING: FAILURE OF MIBG SCAN TO DETECT A BENIGN TRANSFORMATION OF SOFT-TISSUE MALIGNANCY IN THREE CHILDREN

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Poster #103 3461555

SELINEXOR IS MORE ACTIVE THAN DOXORUBICIN IN PATIENT-DERIVED XENOGRAFTS OF DEDIFFERENTIATED LIPOSARCOMA

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Poster #104 3461563

AN UPDATED ANALYSIS OF THE CLINICAL EFFICACY AND SAFETY OF ENTRECTINIB IN NTRK FUSION-POSITIVE (NTRK-FP) SARCOMA

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Poster #105 3461635

LAROTRECTINIB EFFICACY AND SAFETY IN ADULT PATIENTS WITH TRK FUSION SARCOMAS

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Poster #106 3461675

IMPACT OF NEXT GENERATION SEQUENCING (NGS) ON THE TREATMENT OF PATIENTS WITH SARCOMA

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Poster #107 3461682

HISTOLOGY AND TUMOUR BIOLOGY ARE MORE IMPORTANT IN PREDICTING OVERALL SURVIVAL THAN MARGINS OF RESECTION

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Poster #108 3461698

HISTOLOGIC MARKERS PREDICTIVE OF WOUND HEALING COMPLICATIONS IN SOFT TISSUE SARCOMA TREATED WITH PREOPERATIVE RADIATION

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Poster #109 3461710

INTEGRATED SAFETY ANALYSIS OF TAZEMETOSTAT 800 MG TWICE DAILY IN ADULT PATIENTS WITH HEMATOLOGIC AND SOLID TUMORS

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Poster #110 3461748

RECRUITMENT PATTERNS IN A LARGE INTERNATIONAL RANDOMIZED CONTROLLED TRIAL OF PERIOPERATIVE CARE IN CANCER PATIENTS

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Poster #111 3461782

FACTORS INFLUENCING UNPLANNED READMISSION AFTER SURGERY IN SOFT TISSUE SARCOMAS

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Poster #112 3461852

18F-FDG PET/CT CAN HELP SOLVE THE GRADING DILEMMAS IN CARTILAGE BONE NEOPLASMS? SURGEON'S INTERPRETATION FOR TREATMENT PLANNING

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Poster #113 3461875

CLINICOPATHOLOGICAL FEATURES AND TREATMENT OUTCOME OF OESOPHAGEAL GASTROINTESTINAL STROMAL TUMOUR (GIST): A LARGE, RETROSPECTIVE MULTICENTER EUROPEAN STUDY

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Poster #114 3461883

AVAPRITINIB VS REGORAFENIB IN PATIENTS WITH LOCALLY ADVANCED UNRESECTABLE OR METASTATIC GASTROINTESTINAL STROMAL TUMOR (GIST): EFFICACY AND SAFETY DATA FROM PHASE 3 VOYAGER STUDY

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Poster #115 3462029

LAROTRECTINIB EFFICACY AND SAFETY IN PEDIATRIC PATIENTS WITH TRK FUSION SARCOMAS

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Poster #116 3462147

MANAGEMENT OF HEMANGIOENDOTHELIOMA AT A DEDICATED SARCOMA CLINIC IN INDIA: TIME TO LOOK TOWARDS ANTI-ANGIOGENIC THERAPY

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Poster #117 3462149

MODELING THE EFFICACY OF NY-ESO-1 TCR T CELLS (LETETRESGENE AUTOLEUCEL; GSK3377794) IN PATIENTS WITH SYNOVIAL SARCOMA: CORRELATIONS OF RESPONSE WITH TRANSDUCED CELL KINETICS AND BIOMARKERS

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Poster #118 3462192

CAN PATIENTS AT HIGH RISK FOR R2 RESECTION OF RETROPERITONEAL SARCOMA (RPS) BE IDENTIFIED PREOPERATIVELY?

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Poster #119 3462260

ADDED VALUE OF SURGICAL NAVIGATION FOR CHALLENGING INTRA-ABDOMINAL OR PELVIC SARCOMA

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Poster #120 3462325

MANAGEMENT OF HIGH-GRADE EXTREMITY SOFT TISSUE SARCOMAS: AN EXPERT SURVEY

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Poster #121 3462376

COMPLETE PATHOLOGICAL RESPONSE TO NEOADJUVANT TREATMENT IS ASSOCIATED WITH BETTER SURVIVAL OUTCOMES IN PATIENTS WITH SOFT TISSUE SARCOMA

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Poster #122 3462419

OVERALL SURVIVAL AFTER PERIOPERATIVE CHEMOTHERAPY IN THE MANAGEMENT OF PULMONARY METASTASIS IN OSTEOSARCOMA

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Poster #123 3462424

PRECLINICAL ASSESSMENT AND ANALYSIS OF ANTI-SEMA4D TREATMENT FOR OSTEOSARCOMA

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Poster #124 3462442

NCI PROTOCOL 10330: A PHASE 2 STUDY OF BELINOSTAT AND SGI-110 (GUADECITABINE) FOR THE TREATMENT OF UNRESECTABLE AND METASTATIC CONVENTIONAL CHONDROSARCOMA

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Poster #125 3462457

D-3-PHOSPHOGLYCERATE DEHYDROGENASE (PHGDH) INHIBITION DRIVES PRO-SURVIVAL MTOR DEPENDENCY IN OSTEOSARCOMA

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TARGETING PARACRINE FIBROBLASTIC NETWORKS IN GASTROINTESTINAL STROMAL TUMOR INHIBITS CANCER GROWTH AND METASTASIS

Hyunho Yoon[1], *Chih-Min Tang*[1], *Sudeep Banerjee*[2], *Mayra Yebra*[1], *Sangkyu Noh*[1], *Adam M. Burgoyne*[1], *Jorge De la Torre*[1], *Martina De Siena*[1], *Mengyuan Liu*[3], *Lilli Klug*[4], *Yoon Young Choi*[5], *Antonio Delgado*[1], *Zhiyong Wang*[5], *Randall P. French*[1], *Andrew M. Lowy*[1], *Ronald deMatteo*[3], *Michael Heinrich*[4], *Alfredo A. Molinolo*[5], *J. Silvio Gutkind*[5], *Olivier Harismendy*[5], *Jason K. Sicklick*[1]

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Taylor D. Ottesen[1], *Blake S. Shultz*[1], *Alana M. Munger*[1], *Cosmas Sibindi*[1], *Alp Yurter*[1], *Arya R. Varthi*[1], *Jonathan N. Grauer*[1]
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Rishi Trikha[1], *Danielle Greig*[1], *Troy Sekimura*[1], *Michael Arnold*[1], *Alexandra Stavrakis*[1], *Jeffrey Eckardt*[1], *Nicholas Bernthal*[1]
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Elizabeth T. Loggers[1], *Michael J. Wagner*[3], *Bonny Chau*[2], *Seth Pollack*[1], *Matthew J. Thompson*[3], *Edward Kim*[3], *Gabrielle Kane*[3], *Jared Harwood*[3], *Teresa Kim*[3], *Lee D. Cranmer*[3]
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Rishi Trikha[1], *Danielle Greig*[1], *Troy Sekimura*[1], *Jeffrey Eckardt*[1], *Nicholas Bernthal*[1]
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GEMCITABINE-CONTAINING REGIMENS FOR THE TREATMENT OF METASTATIC MYXOFIBROSARCOMA REFRACTORY TO DOXORUBICIN

Arielle Elkrief[1], *Suzanne Kazandjian*[1], *Thierry Alcindor*[1]
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TNT: A PHASE 2 STUDY USING TALIMOGENE LAHERPAREPVEC, NIVOLUMAB AND TRABECTEDIN AS FIRST, SECOND/THIRD LINE THERAPY FOR ADVANCED SOFT TISSUE SARCOMA, INCLUDING DESMOID TUMOR AND CHORDOMA [NCT03886311]

Sant P. Chawla[1], *Victoria Chua-Alcala*[1], *Ted T. Kim*[1], *Kelly Wang*[1], *Paul S. Dy*[1], *Nicole L. Angel*[1], *Micaela K. Paz*[1], *Ania M. Moradkhani*[1], *Doris M. Quon*[1], *Steven M. Wong*[1], *Omid Jafari*[1], *Erlinda M. Gordon*[1]
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THE PROGNOSTIC IMPORTANCE OF PATHOLOGIC FRACTURE IN LIMB SALVAGE SURGERY FOR CHONDROSARCOMA

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ASEPTIC LOOSENING FOLLOWING LIMB SALVAGE SURGERY FOR TUMOR: A REVIEW OF 245 PRIMARY CEMENTED STEM DISTAL FEMORAL REPLACEMENTS IMPLANTED OVER A 40-YEAR PERIOD

Danielle Greig[1], *Rishi Trikha*[1], *Samuel Clarkson*[1], *Troy Sekimura*[1], *Adam A. Sassoon*[1], *Jeffrey Eckardt*[1], *Nicholas Bernthal*[1]
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THE OUTCOMES AND PROGNOSTIC FACTORS IN PATIENTS WITH OSTEOASRCOMA ACCORDING TO AGE* A JAPANESE NATIONWIDE STUDY WITH FOCUSING ON THE AGE DIFFERENCES

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COMBINING SHELF OSTEOTOMY WITH PROXIMAL FEMORAL RECONSTRUCTION AFTER ONCOLOGIC RESECTION

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COMPREHENSIVE MASSIVELY PARALLEL SEQUENCING OF SARCOMAS: EXPERIENCE FROM AN AUSTRALIAN TERTIARY HOSPITAL LABORATORY AND STATE SARCOMA SERVICE

Daniel Wong[1], *Tindaro Giardina*[1], *Cleo Robinson*[1], *Marc Thomas*[1], *Timothy Humphries*[2], *Peter Robbins*[1], *Anne Long*[2], *Michael Millward*[2], *Richard Carey-Smith*[3], *Benhur Amanuel*[1]
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TARGETING CYCLIN DEPENDENT KINASE 8 IN FUSION POSITIVE RHABDOMYOSARCOMA

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Poster #144 3463166

CLINICAL BENEFIT WITH RIPRETINIB AS ≥4TH LINE TREATMENT IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR: UPDATE FROM THE PHASE 3 INVICTUS STUDY

Hans Gelderblom[1], *Michael Heinrich*[2], *Suzanne George*[3], *John Zalcberg*[4], *Sebastian Bauer*[5], *Patrick Schöffski*[6], *César Serrano*[7], *Robin L. Jones*[8], *Steven Attia*[9], *Gina D'amato*[10], *Ping Chi*[11], *Peter Reichardt*[12], *Julie Meade*[13], *Vienna L. Reichert*[13], *Kelvin Shi*[13], *Rodrigo Ruiz-Soto*[13], *Margaret von Mehren*[14], *Jean-Yves Blay*[15]
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Poster #145 3463185

INCIDENCE OF SARS-COV-2 IN PEDIATRIC ONCOLOGY CLINIC AT THE EPICENTER OF THE PANDEMIC

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Poster #146 3463241

DEDIFFERENTIATION WITHIN A WELL DIFFERENTIATED LIPOSARCOMA OF THE EXTREMITY OR TRUNK – IMPLICATIONS FOR CLINICAL MANAGEMENT

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Poster #147 3463247

LOCAL RECURRENCE OF SOFT TISSUE SARCOMA REVISITED: IS THERE A ROLE FOR "SELECTIVE" RADIATION?

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Poster #148 3463515

A NOVEL METHOD FOR THREE-DIMENSIONAL GROWTH AND ASSAY OF PAX3-FOXO1 FUSION-POSITIVE RHABDOMYOSARCOMA CELLS ENRICHES IN CANCER STEM CELL CHARACTERISTICS

Kristianne M. Oristian[1], *Katherine Slemmons*[1], *Michael Deel*[2], *Yi-Tzu Lin*[2], *Napasorn Kuprasertkul*[3], *Lisa Crose*[2], *Katia Genadry*[2], *Po-Han Chen*[4], *Jen-Tsan Ashley Chi*[4], *Corinne Linardic*[2]
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Poster #149 3463549

ARID1A DELETION ENHANCES OSTEOSARCOMAGENESIS IN HUMAN CELL LINES AND MURINE MODEL

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Poster #150 3463551

EFFICACY AND SAFETY OF TAZEMETOSTAT IN PATIENTS WITH INI1/SMARCB1- OR BRG1/SMARCA4-NEGATIVE TUMORS, OR RELAPSED/REFRACTORY SYNOVIAL SARCOMA

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BIOMARKERS FOR DELTAREX-G, THE SAFER CHECKPOINT INHIBITOR FOR SARCOMA: A SINGLE CENTER EXPERIENCE

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Poster #152 3463590

TARGETING SPHINGOLIPID METABOLISM IN SYNOVIAL SARCOMA

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Poster #153 3463619

30-YEAR FOLLOW-UP RESULTS OF 170 CEMENTED ENDOPROSTHETIC RECONSTRUCTIONS FOR TUMORS OF THE UPPER EXTREMITY

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Poster #154 3463673

ACIDIC MICROENVIRONMENTS IN SOFT TISSUE SARCOMA PROMOTES FOXM1 EXPRESSION AND TUMORIGENESIS

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Poster #155 3463677

KAPOSI SARCOMA AFTER SOLID ORGAN TRANSPLANTATION, A SINGLE CENTRE EXPERIENCE

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Poster #156 3463723

NEOADJUVANT CHEMORADIOTHERAPY IN ADVANCED SOFT TISSUE SARCOMA: NASAR STUDY

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GENOMIC LANDSCAPE OF METASTATIC SOFT TISSUE SARCOMA

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Poster #158 3463788

IDENTIFICATION AND AUTHENTICATION OF A NOVEL "FET/ETS" FUSION ONCOPROTEIN IN EWING SARCOMA

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Poster #159 3463800

CUTANEOUS ANGIOSARCOMA: CLINICAL AND MOLECULAR PROFILE AND IMMUNOTHERAPY IN A CASE SERIES

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Poster #160 3463802

FEWER THAN TWO PULMONARY MICRONODULES IDENTIFIED ON PRESENTATION IN PATIENTS WITH OSTEOSARCOMA HAVE NO EFFECT ON 5 YEAR OVERALL SURVIVAL

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Poster #161 3463844

MALIC ENZYME 1 ABSENCE IN SYNOVIAL SARCOMA ALTERS GLUCOSE METABOLISM AND THE GLUTATHIONE-THIOREDOXIN AXIS

Caitlyn B. Brashears[1], *Bethany Prudner*[1], *Richa Rathore*[1], *Anthony Robinson*[1], *Brian A. Van Tine*[1]

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Poster #162 3463876

PROXIMAL FEMORAL REPLACEMENT IN THE TREATMENT OF ONCOLOGIC DISORDERS OF THE PROXIMAL FEMUR: THE EXPERIENCE OF A SINGLE INSTITUTION

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Poster #163 3463885

DISTAL FEMORAL REPLACEMENT FOR TREATMENT OF ONCOLOGIC DISORDERS OF THE LOWER EXTREMITY: THE EXPERIENCE OF A SINGLE INSTITUTION

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Poster #164 3463926

LURBINECTEDIN IN COMBINATION WITH IRINOTECAN IN PATIENTS (PTS) WITH SOFT TISSUE SARCOMAS (STS)

Gregory M. Cote[2], *Santiago Ponce*[3], *Alejandro F. Falcon*[4], *Inmaculada Sánchez Simón*[3], *Elisabeth Jimenez*[3], *Rafael Nunez*[1], *Javier Gómez*[1], *Jesús R Fernández*[1], *Martin Cullell-Young*[1], *Carmen Kahatt*[1], *Ali Zeaiter*[1], *Luis Paz-Ares*[3]
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Poster #165 3463955

SPATIAL DETECTION OF CELLULAR CROSS-PRESENTATION AS A PROGNOSTIC TOOL IN SOFT TISSUE SARCOMA

Monika Ehnman[1], *Panagiotis Tsagkozis*[2], *Yanhong Su*[1], *Nicholas P. Tobin*[1], *Okan Gultekin*[3], *Anna Malmerfelt*[1], *Katrine Ingelshed*[3], *Johanna Lundquist*[1], *Wiem Chaabane*[1], *Maya H. Nisancioglu*[1], *Lina W. Leiss*[1], *Arne Östman*[1,4], *Jonas Bergh*[1,5], *Kaisa Lehti*[3,6], *Saikiran Sedimbi*[3], *Felix Haglund*[1]
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Poster #166 3464017

DEMOGRAPHICS AND OUTCOME OF PATIENTS WITH ADULT HEAD AND NECK SARCOMA: THE OTTAWA EXPERIENCE

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Poster #167 3464033

RIPRETINIB DEMONSTRATED ACTIVITY ACROSS ALL KIT/PDGFRA MUTATIONS IN PATIENTS WITH FOURTH-LINE ADVANCED GASTROINTESTINAL STROMAL TUMOR: ANALYSIS FROM THE PHASE 3 INVICTUS STUDY

Patrick Schöffski[1], *Sebastian Bauer*[2], *Michael Heinrich*[3], *Suzanne George*[4], *John Zalcberg*[5], *Hans Gelderblom*[6], *César Serrano*[7], *Robin L. Jones*[8], *Steven Attia*[9], *Gina D'amato*[10], *Ping Chi*[11], *Peter Reichardt*[12], *Julie Meade*[13], *Kelvin Shi*[13], *Ying Su*[13], *Rodrigo Ruiz-Soto*[13], *Margaret von Mehren*[14], *Jean-Yves Blay*[15]
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Poster #168 3464034

REFINING THE APPROACH TO PATIENTS WITH PRIMARY SOFT TISSUE SARCOMA OF THE EXTREMITIES AND TRUNK WALL (ESTSTS): OUTCOME IMPROVEMENT OVER 30 YEARS AT A SINGLE INSTITUTION

Maria Danieli[2], *Francesco Barretta*[1], *Marco Fiore*[2], *Stefano Radaelli*[2], *Claudia Sangalli*[4], *Marta Barisella*[5], *Silvia Stacchiotti*[3], *Elena Palassini*[3], *Rosalba Miceli*[1], *Dario Callegaro*[2], *Paolo Giovanni Casali*[3], *Alessandro Gronchi*[2]
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Poster #169 3464091

CARDIOTOXICITY AMONG PATIENTS WITH SARCOMA TREATED WITH DOXORUBICN: A REAL-WORLD DATABASE STUDY

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Poster #170 3464158

NOVEL GENE FUSIONS IN PEDIATRIC RHABDOMYOSARCOMAS

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Poster #171 3464160

A NOVEL PATIENT-DERIVED, AGGRESSIVE, EXTRAOSSEOUS EWING SARCOMA CELL LINE

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Poster #172 3464216

SOFT-TISSUE SARCOMA IN ELDERLY PATIENTS: PATTERNS OF CARE AND SURVIVAL

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Poster #173 3464222

THE FREQUENCY OF TP53 GERMLINE PATHOGENIC VARIANTS IN RHABDOMYOSARCOMA EXHIBITING ANAPLASIA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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Poster #174 3464228

OSTEOSARCOMA HEALTH LITERACY: A QUANTITATIVE ASSESSMENT OF ONLINE PATIENT EDUCATION MATERIAL

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Poster #175 3464247

DEMOGRAPHICS AND OUTCOME OF PATIENTS WITH GYNAE SARCOMA (GS), THE OTTAWA EXPERIENCE

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Poster #176 3464274

MIFAMURTIDE CUMULATIVE DOSE AND PROGNOSIS IN THE ADJUVANT TREATMENT OF PATIENTS WITH NON METASTATIC EXTREMITY HIGH GRADE OSTEOSARCOMA: RESULTS OF THE ITALIAN SARCOMA GROUP (ISG), MULTICENTRIC, PROSPECTIVE, ISG/OS-2 TRIAL

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Poster #177 3464351

PAZOPANIB IN METASTATIC BONE SARCOMAS - A UNICENTRIC RETROSPECTIVE ANALYSIS AT A TERTIARY UNIVERSITY HOSPITAL

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Poster #178 3464362

PROGNOSIS OF PATIENTS WITH GENITO-URINARY SOFT TISSUE SARCOMAS (GUSTS), 10 YEARS EXPERIENCES IN A TERTIARY CARE CANCER CENTRE.

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Poster #179 3464399

RADIATION-INDUCED SARCOMA: A RETROSPECTIV POPULATION-BASED STUDY OVER 34 YEARS IN A SINGLE INSTITUTION

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Poster #180 3464414

FAVORABLE INITIAL TUMOR RESPONSE WITH COMBINATION CABOZANTINIB AND NIVOLUMAB IN STAGE 4 ALVEOLAR SOFT PART SARCOMA

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Poster #181 3464415

UNDERSTANDING A RARE SUBTYPE: A REVIEW OF 46 PATIENTS WITH GASTROINTESTINAL LEIOMYOSARCOMA TREATED AT A TERTIARY CARE CENTRE

Alannah Smrke[1], *Myles Smith*[1], *Dirk Strauss*[1], *Andrew Hayes*[1], *Khin Thway*[1], *Cyril Fisher*[2], *Christina Messiou*[1], *Charlotte Benson*[1], *Robin L. Jones*[1]
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Poster #182 3464422

POSTERIOR KNEE ARTHROSCOPY FOR PIGMENTED VILLONODULAR SYNOVITIS UTILIZING ULTRASOUND GUIDANCE

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Poster #183 3464440

USE OF MAGNETIC GROWING INTRAMEDULLARY NAILS WITH INTERCALARY ALLOGRAFT RECONSTRUCTION AFTER TUMOR RESECTION

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Poster #184 3464444

ONCOLOGIC INDICATIONS FOR ELECTROMAGNETIC INTRAMEDULLARY NAILS

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Poster #185 3464465

SUPPORTING CLINICAL DECISION-MAKING FOR PI3K/AKT/MTOR INHIBITORS FOR HIGH-RISK PAEDIATRIC AND AYA SARCOMA

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Poster #186 3464494

ADJUVANT PALBOCICLIB FOR THE PREVENTION OF LOCAL RECURRENCE IN RESECTED LIPOSARCOMA

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Poster #187 3464514

EARLY DIAGNOSIS OF UTERINE SARCOMA IS ASSOCIATED WITH GRAVIDITY, PARITY, AND HISPANIC ETHNICITY

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Poster #188 3464550

TRANSFORMED CANINE AND MURINE MESENCHYMAL STEM CELLS AS A MODEL FOR HIGH GRADE SARCOMA WITH COMPLEX GENOMICS

Natasja Franceschini[1], *Bas Verbruggen*[1], *Marianna Tryfonidou*[2], *Alwine B. Kruisselbrink*[1], *Hans Baelde*[1], *Karin de Visser*[3], *Karoly Szuhai*[1], *Anne-Marie Cleton-Jansen*[1], *Judith V. Bovee*[1]
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Poster #189 3464563

PATIENT ADVOCATES TRANSFORMING SARCOMA CARE IN INDIA

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Poster #190 3464611

CHARACTERIZING THE EFFICACY OF IMMUNE CHECKPOINT INHIBITOR-BASED TREATMENT IN SELECTIVE SUBTYPES OF ADVANCED SARCOMA PATIENTS

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Poster #191 3464643

IMMUNE-MATRIX GENE EXPRESSION SIGNATURES OF CYTOKINES, CHEMOKINES, IMMUNE CHECKPOINTS, MATRIX METALLOPROTEINASES AND TISSUE INHIBITORS OF METALLOPROTEINASES IN FORMALIN-FIXED PARAFFIN-EMBEDDED HUMAN CHONDROSARCOMA SAMPLES

Paulo Rodrigues-Santos[2], *Patricia Couceiro[2], Jani Sofia Almeida[1], Paulo Freitas-Tavares[3], José Manuel Casanova[3]*
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Poster #192 3464670

THE MUSCULOSKELETAL TUMOR REGISTRY: LESSONS, BARRIERS, AND FUTURE GOALS

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Poster #193 3464730

PATTERN OF PRESENTATIONS, OUTCOME OF TREATMENT, AND PATTERN OF FAILURE OF PATIENTS WITH GASTROINTESTINAL ADULT SOFT TISSUE SARCOMAS: A 10 YEARS' EXPERIENCE IN A TERTIARY CANCER CENTRE

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Poster #194 3464830

ASSOCIATIONS OF KNOWN SUSCEPTIBILITY LOCI AND GENETIC ANCESTRY ON EWING SARCOMA RISK IN LATINOS

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Poster #195 3464895

DETERMINING THE CONTRIBUTIONS OF GENES CO-EXPRESSED WITH PD-L1 IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS) CASES IN THE TUMOUR-IMMUNE MICROENVIRONMENT

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Poster #196 3464925

SARCOMA OF BONE ABOUT THE KNEE AND LIMB LENGTH IN PRE-ADOLESCENT PATIENTS: ALL OPTIONS STILL ON THE TABLE

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Poster #197 3464936
REPEAT SURGICAL RESECTION FOR PATIENTS WITH RE-RECURRENT RETROPERITONEAL LIPOSARCOMA
Wenqing Liu[1], *Jun Chen*[1], *Chengli Miao*[1], *Mei Huang*[1], *Yue Hu*[2], *Chenghua Luo*[1]
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Poster #198
WITHDRAWN

Poster #199 3464982
***ATRX* PROMOTES AGGRESSIVE FEATURES OF OSTEOSARCOMA ACROSS SPECIES**
Suzanne Bartholf DeWitt[1], *Sarah Hoskinson*[1], *Dharshan Sivaraj*[1], *Elaina J. Martz*[1], *Maya Sheth*[1], *Hailey E. Brighton*[1], *Robert W. Floyd*[2], *Brian E. Brigman*[1], *Ben Alman*[1], *Jason A. Somarelli*[2], *William C. Eward*[1]
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Tomás J. Soulé[1], *Federico Waisberg*[1], *Martin Angel*[1], *Andres Rodriguez*[1], *Yanina Pfluger*[1], *Matias Chacon*[1]
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Lee D. Cranmer[1], *Elizabeth T. Loggers*[2], *Seth Pollack*[2], *Roxanne O. Moore*[1], *Sarah Duffy*[1], *Michael J. Wagner*[1]
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Erlinda M. Gordon[1], *Victoria Chua-Alcala*[1], *Kelly Wang*[1], *Paul S. Dy*[1], *Micaela K. Paz*[1], *Ted T. Kim*[1], *Nicole L. Angel*[1], *Ania M. Moradkhani*[1], *Omid Jafari*[1], *Doris M. Quon*[1], *Steven M. Wong*[1], *William Tseng*[2], *Sant P. Chawla*[1]
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Poster #205 3465091

LANDSCAPE OF ALK FUSIONS IN SOFT-TISSUE SARCOMAS (STS)

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Poster #206 3465105

ANGIOSARCOMA TREATMENT USING PROPRANOLOL: A SINGLE INSTITUTION EXPERIENCE IN ARGENTINA

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Poster #207 3465109

SQ3370, A NOVEL APPROACH TO LOCALLY CAPTURE AND ACTIVATE CYTOTOXIC DRUGS, PRODUCES SUSTAINED RESPONSES IN INJECTED AND NON-INJECTED LESIONS VIA IMMUNE ACTIVATION IN PRECLINICAL MODELS

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Poster #208 3465112

EWS/FLI DRIVES DYNAMIC REORGANIZATION OF LSD1 AND REST IN EWING SARCOMA CELLS

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Poster #209 3465136

HEAD AND NECK ALVEOLAR RHABDOMYOSARCOMA – A RARE ENTITY

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Poster #210 3465158

PROMIS-10 SURVEY T-SCORES AND UNPLANNED HOSPITAL ADMISSION/EMERGENCY ROOM VISITS

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Poster #211 3465174

SORAFENIB IN DESMOID TUMOR: A BRAZILIAN CANCER CENTER EXPERIENCE

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SILVER-COATED MEGAPROTHESES IN THE MITIGATION OF PROSTHETIC JOINT INFECTIONS – A COST-EFFECTIVENESS ANALYSIS

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Poster #213 3465226

LEVERAGING EVOLUTIONARY FITNESS BOTTLENECKS AS THERAPEUTIC VULNERABILITIES IN DOXORUBICIN-RESISTANT OSTEOSARCOMA

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Poster #214 3465233

ADJUNCT DIAGNOSTIC STRATEGIES IN IMPROVING DIAGNOSTIC YIELDS IN IMAGE-GUIDED BIOPSIES – A COST-EFFECTIVENESS ANALYSIS

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Poster #215 3465243

CIRCULATING TUMOR DNA IN CYTOGENETICALLY COMPLEX SOFT TISSUE SARCOMAS

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Poster #216 3465258

EVALUATION OF PATIENT AND HEALTHCARE PROVIDER KNOWLEDGE, ATTITUDES, AND BEHAVIOR (KAB) FOR SAFETY AND USE OF PEXIDARTINIB

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Poster #217 3465259

PATIENT-DERIVED SARCOMA MODELS TOWARDS NOVEL BIOLOGY AND TREATMENT

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Poster #218 3465280

OUTCOMES OF WOUND HEALING WITH A TOPICAL SKIN ADHESIVE AFTER TUMOR RESECTION

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Poster #219 3465283

A NEW INDUCIBLE ZEBRAFISH MODEL OF EWING SARCOMA REVEALS THE IMPORTANCE OF ECM IN DEVELOPMENT OF THE DISEASE

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Poster #220 3465290

SQ3370-001: A MULTI-CENTER, OPEN-LABEL PHASE I DOSE-ESCALATION STUDY OF SQ3370, A NOVEL INTRATUMORAL AND SYSTEMIC APPROACH TO ADMINISTER ANTHRACYCLINES FOR TREATING SOFT TISSUE SARCOMAS AND OTHER ADVANCED SOLID TUMORS

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Poster #221 3465303

PEDIATRIC ONCOLOGY PROVIDERS' MENTAL HEALTH IN THE EPICENTER OF THE PANDEMIC, PRELIMINARY REPORT

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Poster #222 3465305

A META-ANALYTIC EVALUATION OF THE CORRELATION BETWEEN SURROGATE ENDPOINTS AND OVERALL SURVIVAL IN RANDOMIZED CONTROLLED TRIALS OF NEWLY DIAGNOSED OSTEOSARCOMA

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Poster #223 3465320

IMMUNE-CHECKPOINT GENES AS PREDICTIVE BIOMARKERS OF TRABECTEDIN IN ADVANCED SOFT-TISSUE SARCOMA (STS): A SPANISH GROUP FOR RESEARCH ON SARCOMAS (GEIS) TRANSLATIONAL STUDY

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Poster #224 3465381

HETEROGENEITY OF CHEMOTHERAPY EFFECT IN HIGH-RISK PATIENTS WITH EXTREMITY SOFT TISSUE SARCOMA

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Poster #225 3465410

DEFINING A TEXTBOOK SURGICAL OUTCOME FOR PATIENTS FOR UNDERGOING SURGICAL RESECTION OF INTERMEDIATE AND HIGH-GRADE SOF TISSUE SARCOMAS OF THE EXTREMITIES

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Poster #226 3465411

FUNCTIONAL CONSEQUENCES OF OVEREXPRESSION OF MIR-26A AND MIR-3913 IN WDLPS AND DDLPS

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Poster #227 3465438

MISMATCH REPAIR DEFICIENCY IN BONE AND SOFT TISSUE TUMORS: IS THERE A RATIONALE FOR ROUTINE TESTING IN ADVANCED SARCOMA?

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Poster #228 3465449

PROGNOSTIC VALUE OF PGP AS STRATIFICATION FACTOR FOR THE TREATMENT OF PATIENTS WITH NON-METASTATIC EXTREMITY HIGH-GRADE OSTEOSARCOMA: A SPANISH SOCIETY OF PEDIATRIC HEMATOLOGY AND ONCOLOGY (SEHOP) AND SPANISH GROUP FOR RESEARCH IN SARCOMAS (GEIS) STUDY

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Poster #229 3465504

LATE CENTRAL NERVOUS SYSTEM AND LUNG RECURRENCE OF EWING'S SARCOMA: A CASE REPORT

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Poster #230 3465518

LYMPHOVASCULAR INVASION AND HISTOPATHOLOGIC PROFILE PORTENDS WORSE PROGNOSIS IN CHONDROSARCOMA

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IMPACT OF PATHOLOGICAL STRATIFICATION OF ADVANCED WELL DIFFERENTIATED/DEDIFFERENTIATED (WD/DD) LIPOSARCOMA (LPS) ON THE RESPONSE TO TRABECTEDIN (T)

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Poster #232 3465550

COMPREHENSIVE IMMUNOPHENOTYPING OF SOFT TISSUE SARCOMA PATIENTS DEFINES ASSOCIATION WITH FUNCTIONALLY DISTINCT LYMPHOCYTE SUBSETS AND MAJOR SUPPRESSOR CELLS

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Poster #233 3465551

ADVANCED DERMATOFIBROSARCOMA PROTUBERANS: EXPERIENCE FROM A SARCOMA CLINIC IN INDIA

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NKT-LIKE CELLS DISPLAY ALTERED PATTERNS OF MATURATION, MIGRATION, ACTIVATION AND EXPRESSION OF IMMUNE CHECKPOINTS IN SOFT TISSUE SARCOMA

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Poster #235 3465580

SOCIOECONOMIC STATUS AND CANCER-RELATED MORTALITY IN SOFT TISSUUE SARCOMA: AN ANLAYSIS OF THE SEER DATABASE

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Poster #236 3465593

USE OF A HUMANIZED XENOGRAFT MURINE MODEL TO CHARACTERIZE THE TREATMENT EFFECT OF CYTOTOXIC CHEMOTHERAPY AND IMMUNOTHERAPY ON OSTEOSARCOMA

Simon Yaguare[1], ***Valentina Viscarret***[1], *Osama Aldahamsheh*[1], *Jichuan Wang*[1], *Hasibagan Borjihan*[1], *Janet Tingling*[1], *Dana Kamens*[1], *Robert Schneider*[1], *Daniel Weiser*[2], *Rui Yang*[1], *Bang Hoang*[1], *David S. Geller*[1]
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Poster #237 3465607

DEVELOPMENT OF AN UPDATED INTERNATIONAL CONSENSUS ON THE MANAGEMENT OF PRIMARY RETROPERITONEAL SARCOMA (RPS) BY TARPSWG

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Poster #238 3465625

THE INTERACTION OF SKP2 WITH P27 ENHANCES IN THE PROGRESSION AND TUMOR-INITIATING PROPERTIES OF OSTEOSARCOMA

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Poster #239 3465637

LONG-TERM RESULTS OF ADJUVANT MIFAMURTIDE ALONGSIDE CHEMOTHERAPY IN THE TREATMENT OF PEDIATRIC AND ADULT PATIENTS WITH OSTEOSARCOMA

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Poster #240 3465660

ACCURACY OF X-RAY AND MAGNETIC RESONANCE IMAGING IN DEFINING THE TUMOR MARGIN IN PRIMARY BONE SARCOMA

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Poster #241 3465668

IDENTIFICATION AND EVALUATION OF NOVEL RHABDOMYOSARCOMA ANTIGENS FOR USE IN ONCOLYTIC VACCINES

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Poster #242 3465674

PILOT STUDY OF THE EFFECT OF HIGH DOSES OF RADIATION ON BONE METABOLISM AND STRUCTURE IN PATIENTS TREATED WITH ADJUVANT RADIOTHERAPY AND SURGERY FOR SACRAL TUMORS.

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Poster #243 3465693

NEURONAL INFLUENCES IN AN UNDIFFERENTIATED TUMOR: THE NERVOUS MICROENVIRONMENT OF UNDIFFERENTIATED PLEOMORPHIC SARCOMA

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Poster #244 3465698

EVALUATION OF CANCER-TESTIS ANTIGENS IN OSTEOSRACOMA AND DEDIFFRETIATIED LIPOSARCOMA AS TARGETS FOR IMMUNOTHERAPY

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Poster #245 3465699

EVALUATION OF BASELINE NEUTROPHIL TO LYMPHOCYTE (NLR), PLATELET TO LYMPHOCYTE (PLR) AND LYMPHOCYTE TO MONOCYTE RATIOS (LMR) AS PROGNOSTIC FACTORS IN OSTEOSARCOMA – THE TORONTO SARCOMA PROGRAM EXPERIENCE

Olubukola Ayodele[1], *Anthony Griffin*[2], *Peter Ferguson*[2], *Abha A. Gupta*[1], *Jay Wunder*[2], *Albiruni Abdul Razak*[1]
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Poster #246

WITHDRAWN

Poster #247 3465718

IMMUNE SIGNATURE AND MOLECULAR PROFILING OF EPITHELIOID HEMANGIOENDOTHELIOMA (EHE): A TORONTO SARCOMA PROGRAM STUDY

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Poster #248 3465772

CAN INTRAOPERATIVE USE OF INDOCYANINE GREEN DYE ANGIOGRAPHY PREDICT RATES OF WOUND COMPLICATIONS IN PATIENTS UNDERGOING SOFT TISSUE RESECTION?

Joanne Zhou[1], *Ann Richey*[1], *Cara Lai*[1], *Subhro Sen*[2], *David Mohler*[1], *Robert Steffner*[1]
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Poster #249 3465776

20-YEAR EXPERIENCE IN THE MANAGEMENT OF PATIENTS WITH EXTRASKELETAL MYXOID CHONDROSARCOMA IN A SARCOMA REFERENCE CENTRE

Robert D. Beveridge[1], *Benjamin Domingo Arrue*[1], *Javier Perea Rojo*[1], *Ana Ferrero*[1], *Nuria Gómez Sepúlveda*[1], *Alba Torres Martinez*[1], *Carlos Puchades Olmos*[1], *Diego Soriano Polo*[1], *Guillermo Suay Montagud*[1], *Julio Linares Diaz*[1]
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Poster #250 3465785

SAFETY OF DISCHARGE AT HIGHER SERUM METHOTREXATE LEVELS IN PEDIATRIC OSTEOSARCOMA PATIENTS

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Poster #251 3465792

IDENTIFYING MODIFIABLE AND NON-MODIFIABLE RISK FACTORS FOR READMISSION AND SHORT TERM MORTALITY IN OSTEOSARCOMA

Alexander L. Lazarides[1], *Daniel Evans*[1], *Mark M. Cullen*[1], *Marcelo Cerullo*[2], *Dan G (Trey) Blazer*[2], *Brian E. Brigman*[1], *William C. Eward*[1]
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Poster #252 3465794

SURVIVAL OUTCOMES IN PATIENTS WITH RETROPERITONEAL SARCOMA (RPS): AN ANALYSIS OF THE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) DATABASE

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Poster #253 3465805

CLINICAL OUTCOMES OF PATIENTS WITH SARCOMA HARBORING TP53 GERMINATIVE MUTATION – A SINGLE CENTER RETROSPECTIVE ANALYSIS

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Poster #254 3465814

WHY DO ORTHOPAEDIC ONCOLOGY PATIENTS UNDERGOING PROSTHETIC RECONSTRUCTION GET READMITTED?

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Poster #255 3465821

DENOSUMAB IN THE MULTIDISCIPLINARY MANAGEMENT OF GIANT-CELL BONE TUMOURS. LONG-TERM EFFICACY AND TOXICITY DATA

Robert D. Beveridge[1], *Alba Torres Martinez*[1], *Carlos Puchades Olmos*[1], *Benjamin Domingo Arrue*[1], *Diego Soriano Polo*[1], *Guillermo Suay Montagud*[1], *Ana Ferrero*[1], *Javier Perea Rojo*[1], *Nuria Gómez Sepúlveda*[1], *Julio Linares Diaz*[1]
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Poster #256 3465823

SYNCHRONOUS CO-LOCALIZATION OF GIST AND PERITONEAL MESOTHELIOMA: A SINGLE INSTITUTION CASE SERIES

Asimina S. Courelli[3], *Yoon Young Choi*[4], *Shirley Sarno*[1], *Kaitlyn Kelly*[1], *Santiago Horgan*[2], *Olivier Harismendy*[4], *Joel Baumgartner*[1], *Jason K. Sicklick*[1]
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Poster #257 3465847

PEDIATRIC NON-MYOFIBROBLASTIC MESENCHYMAL NEOPLASMS WITH ALK AND ROS1 GENE REARRANGEMENTS

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Poster #258 3465855

UPDATED ANALYSIS OF GENETIC ALTERATIONS IN SARCOMA PATIENTS OF HISPANIC AND NON-HISPANIC ETHNICITY: ANALYSIS OF 174 PATIENTS, A SINGLE INSTITUTION EXPERIENCE

Emily E. Jonczak[2], *Caroline Hana*[1], *Andrea Espejo*[1], *Junaid Arshad*[1], *Philippos Costa*[1], *Priscila Barreto-Coelho*[1], *Konstantinos Sdrimas*[1], *Brianna Valdes*[1], *Gina D'amato*[1], *Jonathan Trent*[1]
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Poster #259 3465859

PREOPERATIVE RADIOTHERAPY IN LOWER EXTREMITY SOFT TISSUE SARCOMA TO REDUCE MAJOR WOUND HEALING COMPLICATIONS – THE ROLE OF NORMAL TISSUE DOSE REDUCTION

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Poster #260 3465872

WITHDRAWN

Poster #261 3465888

SUPERIOR MESENTERIC ARTERY BRANCHES AS A READOUT FOR PREDICTING FUTURE SMALL BOWEL LENGTH DURING ABDOMINAL AND RETROPERITONEAL LIPOSARCOMA RESECTIONS

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Poster #262 3465890

THE IMPACT OF RADIATION THERAPY ON SURVIVAL IN MYXOID LIPOSARCOMA

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Poster #263 3465898

DOES ATTACHMENT STYLE (RELATIONSHIP STATUS) IMPACT OUTCOME IN ADULTS WITH SARCOMA?

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Poster #264 3465900

WHAT IS THE LIKELIHOOD OF NON-PULMONARY METASTASIS OCCURRING IN THE ABSENCE OF LUNG METASTASIS IN BONE AND SOFT TISSUE SARCOMA? A NESTED CASE CONTROL STUDY FROM A REFERRAL SARCOMA CENTER

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Poster #265 3465904

SURGICAL MANAGEMENT REMAINS THE BEST PREDICTOR OF SURVIVAL: LESSONS FROM THE NATIONAL CANCER DATABASE (NCDB) IN DESCRIBING CHARACTERISTICS, MANAGEMENT, AND OUTCOMES FOR PATIENTS WITH CHONDROSARCOMA

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Poster #266 3465916

WHAT ARE THE PREDICTORS OF READMISSION AND SHORT TERM MORTALITY IN CHONDROSARCOMA?

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Poster #267 3465927

PROBING THE THERAPEUTIC LANDSCAPE OF CHONDROSARCOMA WITH INTEGRATED CHEMICAL SCREENING

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Poster #268 3465928

RACIAL DISPARITIES BY HISTOLOGY FOR SARCOMAS OF SOFT-TISSUE AND BONE

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Poster #269 3465948

CHARACTERISTICS AND LONG-TERM OUTCOMES OF SURGICALLY MANAGED HIGH-GRADE EXTREMITY CHONDROSARCOMA

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Poster #270 3465964

IMPACT OF CHEMOTHERAPY TREATMENT ON OVERALL SURVIVAL IN DEDIFFERENTIATED CHONDROSARCOMA: AN ANALYSIS OF THE SEER DATABASE

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Poster #271 3466167

A RARE CASE SERIES OF COMPOSITE HEMANGIOENDOTHELIOMA PRESENTING AS BONE TUMOR

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Poster #272 3467206

COMPREHENSIVE COMPLICATION INDEX BETTER ESTIMATES THE IMPACT OF COMPLICATIONS IN RETROPERITONEAL SARCOMA SURGERY COMPARED TO CLAVIEN-DINDO CLASSIFICATION

Fulvia Aymerito[1], *Ferdinando Carlo Maria Cananzi*[1], *Laura Samà*[1], *Laura Ruspi*[2], *Federico Sicoli*[2], *Edoardo A. Baccalini*[3], *Federica Barzaghi*[1], *Vittorio L. Quagliuolo*[2]
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Poster #273 3467207

FOCUSED ULTRASOUND FOR APPENDICULAR SOFT-TISSUE SARCOMAS: TARGETABILITY ASSESSMENT FOR TISSUE-SELECTIVE TREATMENTS

Lauren Mancia[1], *Neffisah D'odoo*[2], *Jess Gannon*[2], *Nathaniel Meyer*[1], *Eli Vlaisavljevich*[2], *Geoffrey W. Siegel*[1]
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Poster #274 3467256

FOSB-ACTB FUSION IN PSEUDOMYOGENIC HEMANGIOENDOTHELIOMA: CASE STUDY OF THE YOUNGEST PEDIATRIC PATIENT.

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Poster #275 3467312

THE AMERICAN COLLEGE OF SURGEONS (ACS) SURGICAL RISK CALCULATOR UNDERESTIMATES THE ACTUAL RISKS OF SURGERY FOR RETROPERITONEAL SARCOMA: RESULTS FROM A REFERRAL CENTER

Laura Samà[1], *Laura Ruspi*[2], *Ferdinando Carlo Maria Cananzi*[1], *Federico Sicoli*[2], *Fulvia Aymerito*[3], *Edoardo A. Baccalini*[3], *Vittorio L. Quagliuolo*[2]
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Poster #276 3467373

WHAT IS THE UTILITY OF CHEST SURVEILLANCE FOR ATYPICAL LIPOMATOUS TUMORS OF THE EXTREMITIES?

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Poster #277 3467404

PREDICTING THE SURVIVAL PROBABILITY AND ASSESSING PROGNOSTIC FACTORS IN PATIENTS WITH MALIGNANT EPITHELIOID HEMANGIOENDOTHELIOMA OF BONE: A POPULATION-BASED ANALYSIS

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Poster #278 3467407

RETREATMENT WITH FIRST LINE DRUGS IN MULTIPLY RELAPSED OSTEOSARCOMA

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Poster #279 3467486

IS LOCAL RECURRENCE IN EXTREMITY SARCOMA JUST A LOCAL RECURRENCE, OR DOES IT IMPACT THE OVERALL SURVIVAL; NESTED CASE CONTROL STUDY FROM A SARCOMA REFERRAL CENTER.

Obada Hasan[1], *Momin Nasir*[2], *Mustafa Hashimi*[2], *Qiang An*[1], *Benjamin J. Miller*[1]
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Poster #280 3467593

NOVEL SCORING CRITERIA FOR PREOPERATIVE PREDICTION OF NEOADJUVANT CHEMOTHERAPY RESPONSE IN OSTEOSARCOMA: A RETROSPECTIVE COHORT STUDY FROM A SARCOMA CENTER

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Poster #001 3412554

DIFFICULTY OF DISTINGUISHING ARTERIAL INTIMAL SARCOMA FROM CHRONIC PULMONARY EMBOLISM THROUGH DIFFERENTIAL DIAGNOSIS

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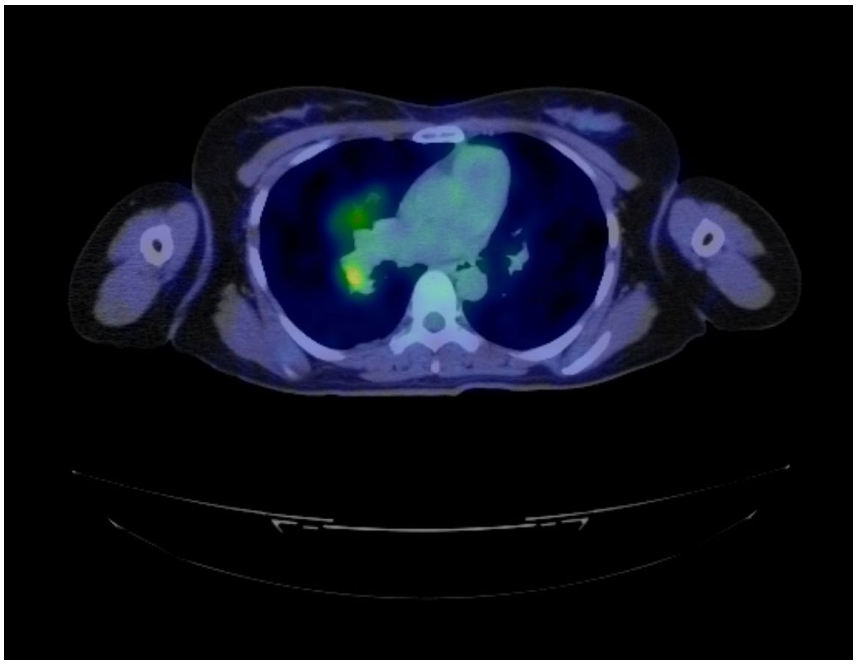
Objective: Pulmonary artery intimal sarcoma is a rare malignant soft tissue tumor that is difficult to distinguish from chronic pulmonary thromboembolism through differential diagnosis. It is challenging to perform biopsies in such cases, and often difficult to make a preoperative diagnosis. However, recently the use of standardized uptake values (SUVs) from fluorodeoxyglucose positron emission tomography (FDG–PET) imaging has allowed the differential diagnosis of pulmonary artery intimal sarcoma from chronic pulmonary thromboembolism and other similar conditions. Here, we report on a case of pulmonary artery intimal sarcoma that was difficult to distinguish from chronic pulmonary thromboembolism, even using FDG–PET imaging.

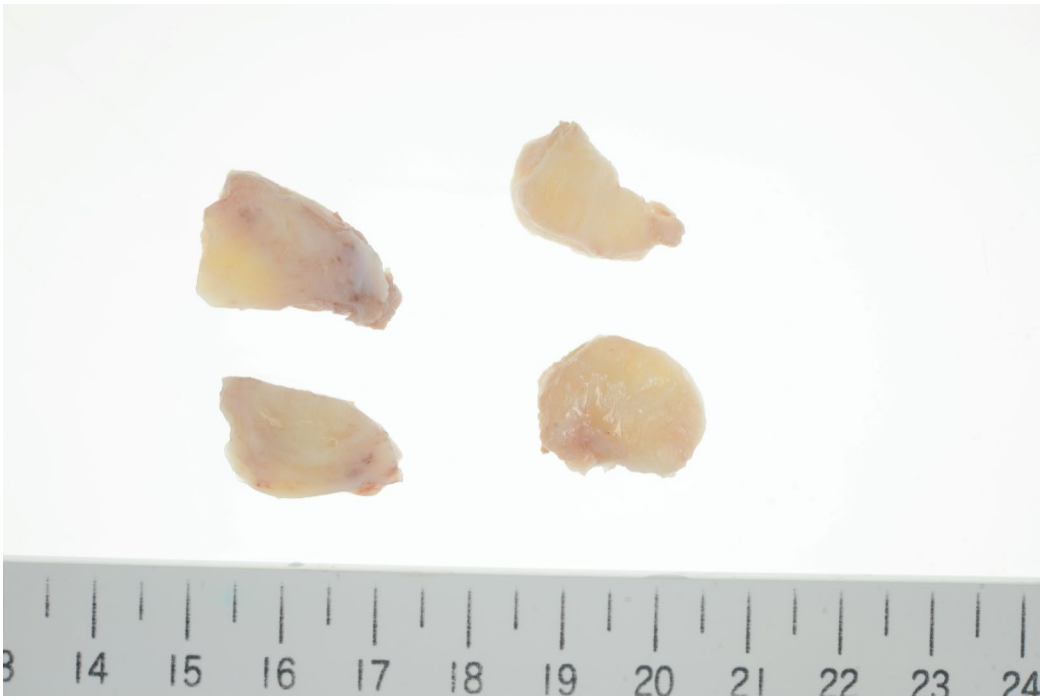
Methods: A 40-year-old woman with exertional dyspnea starting from XX/201Y (month/year) presented to a nearby clinic, but a definite diagnosis was not reached. The patient then visited our hospital 13 months after experiencing her first symptom. Using contrast computed tomography (CT), lesions with mild emission were observed from the right pulmonary artery trunk to the superior lobar branches. A differential diagnosis may include a pulmonary embolism accompanied by a pulmonary artery intimal sarcoma, chronic pulmonary thromboembolism, tumor embolus, and deep vein thrombosis as potential diagnoses.

Results: FDG–PET imaging and an ultrasound scan of the lower limbs did not reveal suspected tumors and/or thrombosis in other body areas. The SUV of the lesions was as low as 3.4. The patient was transferred to another hospital for more specialized medical treatment as well as a differential diagnosis of thrombosis. Cytodiagnosis by right heart catheterization was conducted but a definite diagnosis could not be reached. Pulmonary endarterectomy was then conducted and from the specimen, a diagnosis of intimal sarcoma was made.

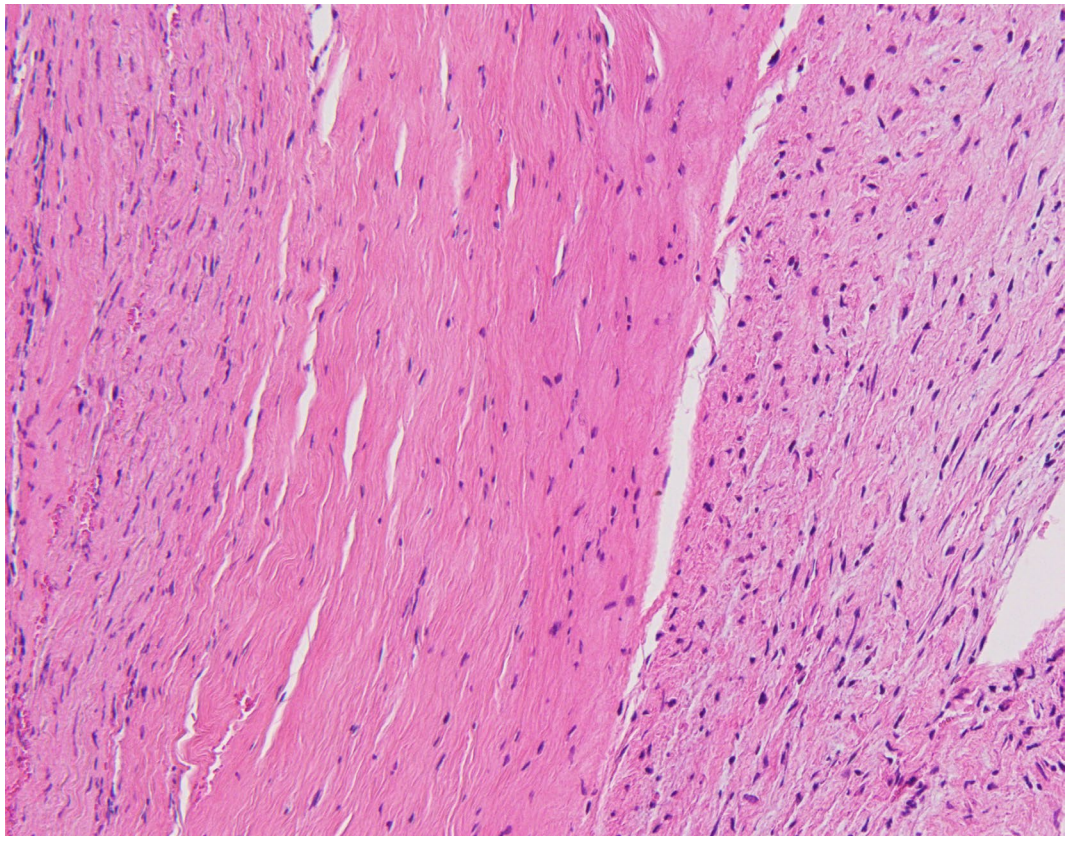
Conclusion: Before FDG–PET imaging was widely used, the preoperative diagnosis of pulmonary artery intimal sarcoma was extremely difficult, with more than 70% of cases diagnosed as pulmonary thromboembolism. With the spread of FDG–PET imaging, the number of cases that are able to be distinguished from other diseases, such as chronic pulmonary thromboembolism, has increased. However, some cases of pulmonary artery intimal sarcoma, which show less cellular density and/or have more mucous tissue, have similar levels of SUVs as chronic pulmonary thromboembolism. This case also showed proliferated spindle-shaped tumor cells with a mucous tumor and edematous stroma, leading to low SUVs. When a case has suspected lesions of pulmonary artery intimal sarcoma with low FDG accumulation, more invasive testing, such as right heart catheterization, and surgical methods specific for pulmonary artery intimal sarcoma should be considered.



PET image



macroscopic image



HE stain

Poster #002 3412790

APATINIB FOR TREATMENT OF INOPERABLE METASTATIC OR LOCALLY ADVANCED CHONDROSARCOMA: WHAT CAN WE LEARN ABOUT THE BIOLOGICAL BEHAVIOR OF CHONDROSARCOMA FROM A MULTICENTER STUDY

Lu Xie[1], *Jie Xu*[1], *Jin Gu*[2], *Zhe Lv*[3], *Xiaodong Tang*[1], *Wei Guo*[1]
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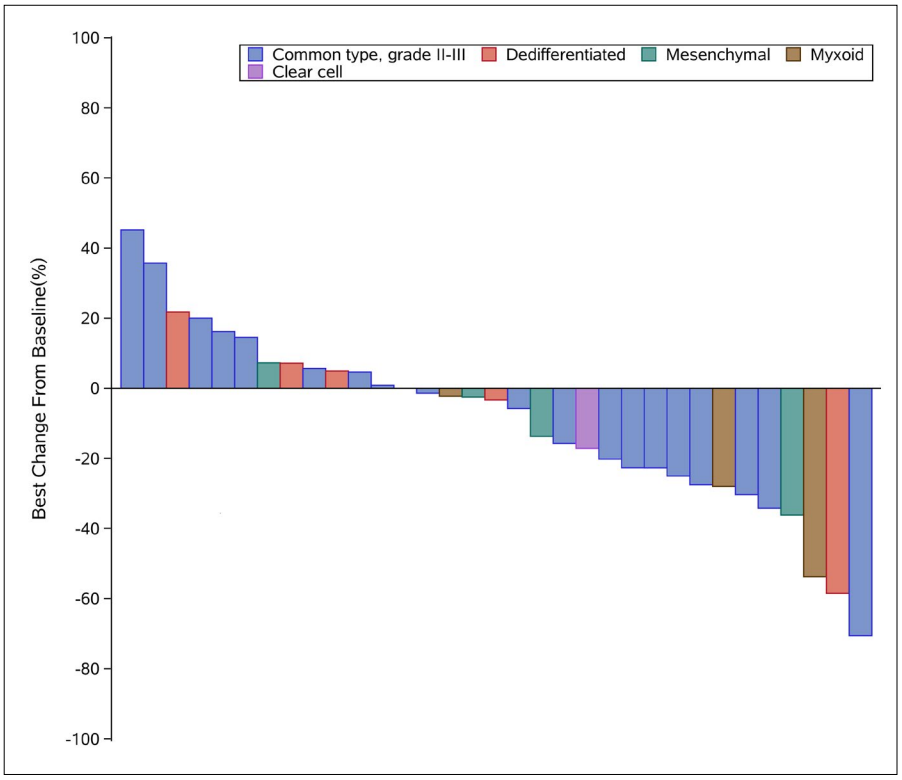
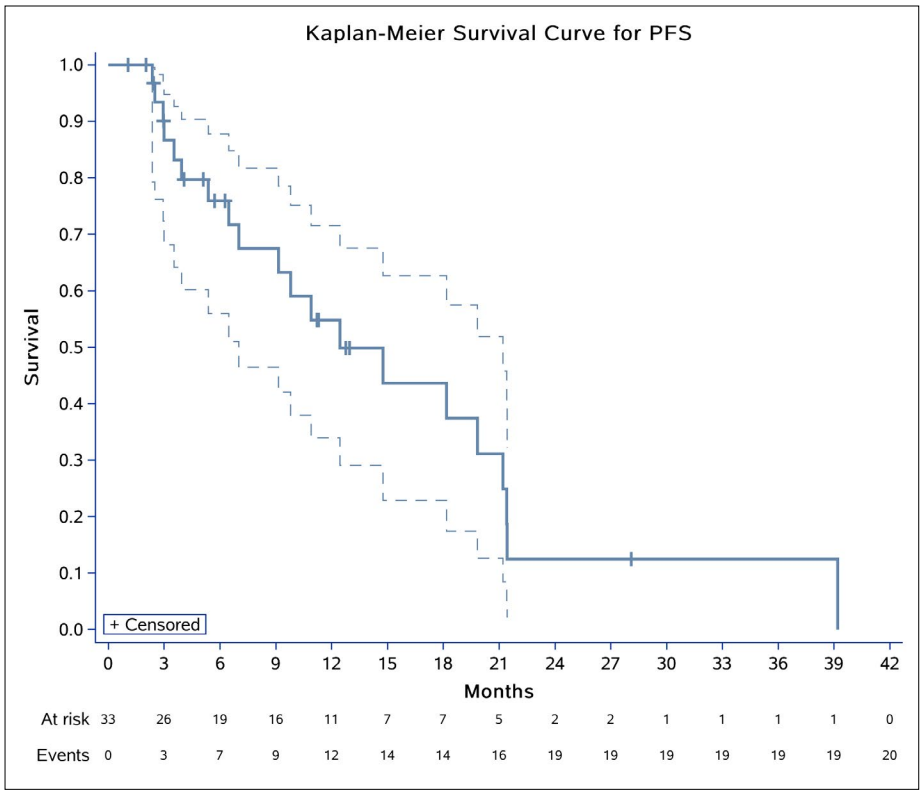
Objective: For patients who have chondrosarcoma in the unresectable setting, antiangiogenic agents are reportedly effective. This multicenter, retrospective study investigated the antitumor activity of apatinib in patients with unresectable chondrosarcoma to gain insight into the biological behavior of this disease.

Methods: All of the patients with unresectable chondrosarcoma who were diagnosed between October 1, 2009, and November 1, 2019, in two sarcoma centers affiliated with Peking University were evaluated. Relevant information was collected from the medical records at both centers, from which patients receiving apatinib for systemic therapy were selected for analysis.

Results: In total, efficacy analysis was conducted in 33 patients with a median follow-up time of 22.1 (Q1, Q3, 14.6, 23.0) months. There were 20/33 (60.0%) conventional chondrosarcomas (grades 2–3), 5/33 (15.2%) dedifferentiated chondrosarcomas, 4/33 (12.1%) mesenchymal chondrosarcomas, 3/33 (9.1%) extraskeletal myxoid chondrosarcoma, and 1/33 (3.1%) clear cell chondrosarcomas with 87.9% in metastatic and 12.1% in locally advanced states. The objective response rate was 6/33 (18.2%). The median progression-free survival (PFS) was 12.4 months (Q1, Q3, 7.0, 21.2), while the median overall survival has not yet been reached. Rare variants of chondrosarcoma tended to have a longer PFS than conventional chondrosarcoma (*P*=0.06). Based on clinicopathological factors Cox and univariate analysis, only extraskeletal myxoid chondrosarcoma and baseline target lesions <60 mm benefited from the drug apatinib (*P*=0.14 and *P*=0.00), respectively. Grade 3 or higher adverse events were frequent in 11/33 (39.3%) of patients who discontinued apatinib due to deterioration of their general condition.

Conclusion: Apatinib had clinically meaningful activity in patients with inoperable high-grade chondrosarcoma. However, special caution should be made in managing toxicity due to the indolent behavior and slow growth pattern after using this drug. Patients with a smaller tumor size and extraskeletal myxoid chondrosarcoma subtype might benefit from this therapy more.




Kaplan-Meier Survival Curve for PFS
Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
+ Censored
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42
Months
At risk 33 26 19 16 11 7 7 5 2 2 1 1 1 1 0
Events 0 3 7 9 12 14 14 16 19 19 19 19 19 19 20

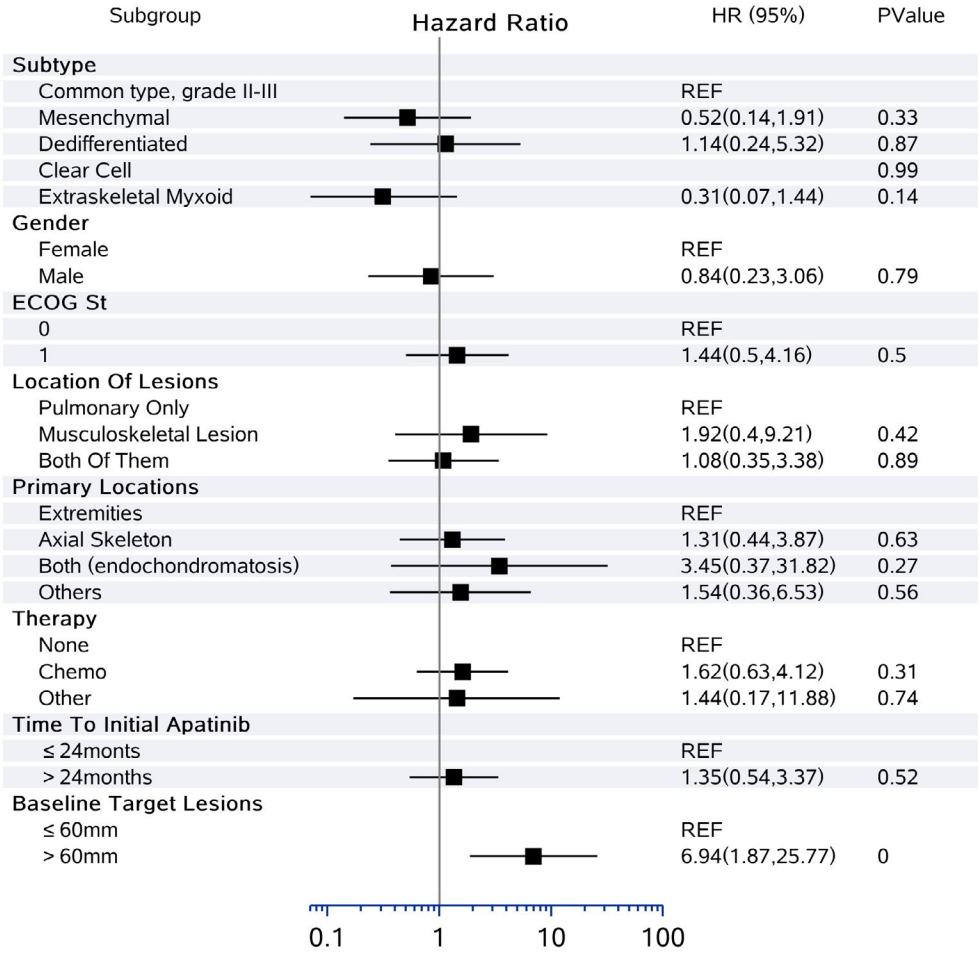

Subgroup
Hazard Ratio
HR (95%)
PValue
Subtype
Common type, grade II-III REF
Mesenchymal 0.52(0.14,1.91) 0.33
Dedifferentiated 1.14(0.24,5.32) 0.87
Clear Cell 0.99
Extraskeletal Myxoid 0.31(0.07,1.44) 0.14
Gender
Female REF
Male 0.84(0.23,3.06) 0.79
ECOG St
0 REF
1 1.44(0.5,4.16) 0.5
Location Of Lesions
Pulmonary Only REF
Musculoskeletal Lesion 1.92(0.4,9.21) 0.42
Both Of Them 1.08(0.35,3.38) 0.89
Primary Locations
Extremities REF
Axial Skeleton 1.31(0.44,3.87) 0.63
Both (endochondromatosis) 3.45(0.37,31.82) 0.27
Others 1.54(0.36,6.53) 0.56
Therapy
None REF
Chemo 1.62(0.63,4.12) 0.31
Other 1.44(0.17,11.88) 0.74
Time To Initial Apatinib
≤ 24monts REF
> 24months 1.35(0.54,3.37) 0.52
Baseline Target Lesions
≤ 60mm REF
> 60mm 6.94(1.87,25.77) 0
0.1
1
10
100

Table 1 Patients' demographics (N=33)

Demographic characteristics	
Age (years; mean ± sd) (95% CI)	40.91±13.61 (36.08, 45.74)
Gender, N (%)	
Male	24 (72.73)
Female	Female 9 (27.27)
Surgeries, median (range)	2 (1, 5)
ECOG performance status at enrollment, N (%)	
0	14 (42.42)
1	19 (57.58)
Subtypes of chondrosarcoma, N (%)	
Common type, grades 2–3	20 (60.61)
Dedifferentiated type	5 (15.15)
Mesenchymal type	4 (12.12)
Extraskeletal myxoid chondrosarcoma	3 (9.09)
Clear cell type	1 (3.03)
Median target lesion size at baseline (95% CI), mm	64.30 (57.59, 91.48)
Locations of lesions before using apatinib, N (%)	
Pulmonary lesions only	9 (27.27)
Musculoskeletal lesions only	4 (12.12)
Both at pulmonary lesions and musculoskeletal lesions as well as visceral infiltration	20 (60.61)
Primary tumor location, N (%)	
Extremities	10 (30.30)
Axial skeleton	19 (57.58)
Multiple lesions (malignancy transformation from endochondromatosis)	1 (3.03)
Maxillofacial region	2 (6.06)
Ribs	1 (3.03)
Time interval from diagnosis to apatinib treatment	
(months; mean ± sd) (95% CI)	19.92±19.87 (12.87, 26.96)
≤24 months, N (%)	16 (48.48)
>24 months, N (%)	17 (51.52)

There are others no included in this table because of short of the table: such as clinical information of Previous antineoplastic treatments, N (%), Prior Radiation, Patients' reason for stopping apatinib, N (%) and so on.

Poster #003 3412794

DYNAMIC CHANGES IN QUALITY OF LIFE AND Q-TWIST ANALYSIS FOR EWING SARCOMA PATIENTS FOLLOWING ANLOTINIB AND IRINOTECAN, A COMBINATION OF PHASE 1B AND 2 TRIAL

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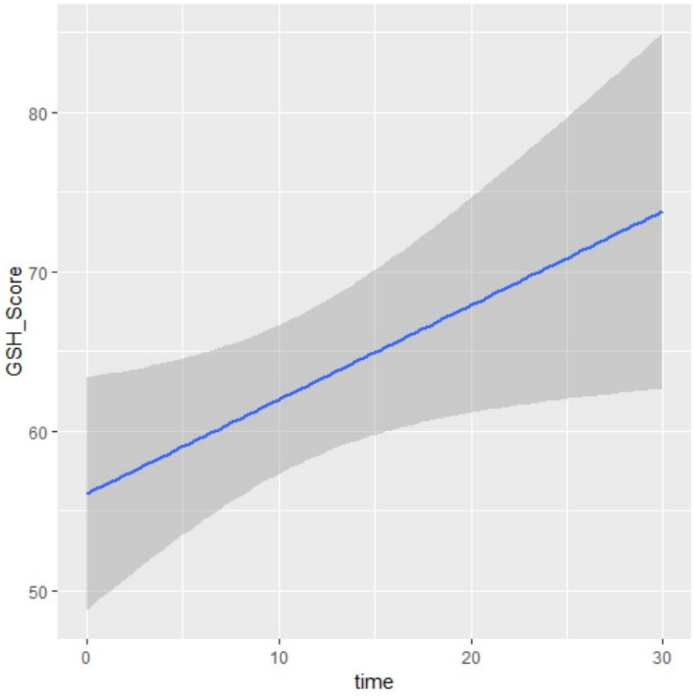
[1]*Musculoskeletal Tumor Center, Peking University People's Hospital, Beijing, Beijing, CHINA*

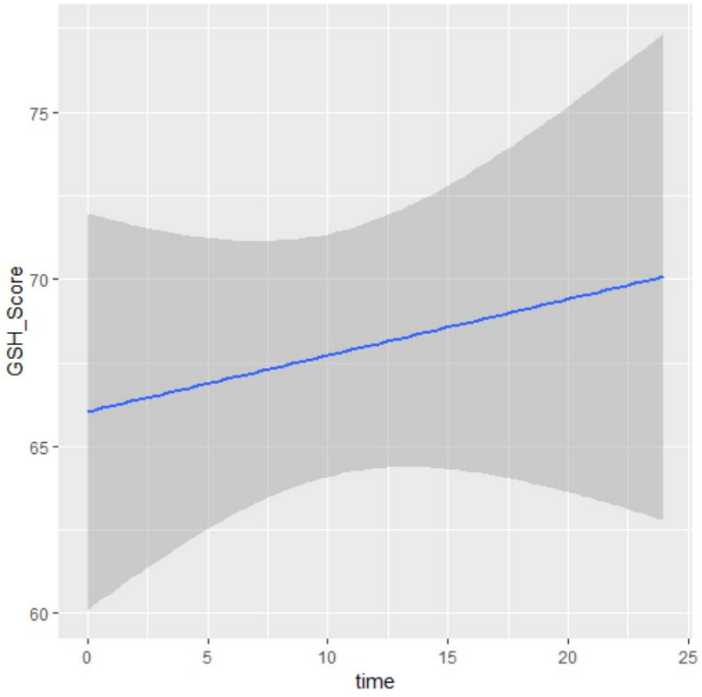
Objective: For advanced Ewing sarcoma (EWS) progression upon first-line chemotherapy, we investigated a novel treatment combination with anti-angiogenesis tyrosine kinase inhibitors (aaTKIs), anlotinib and classic 10-day irinotecan administration strategy in PKUPH-EWS-02. Health-related quality of life (QoL) was an exploratory endpoint in this trial (N=35). The objective of this study was to assess dynamic changes in quality of life (QoL) and determine the benefit-risk in terms of quality-adjusted survival for patients using these therapies.

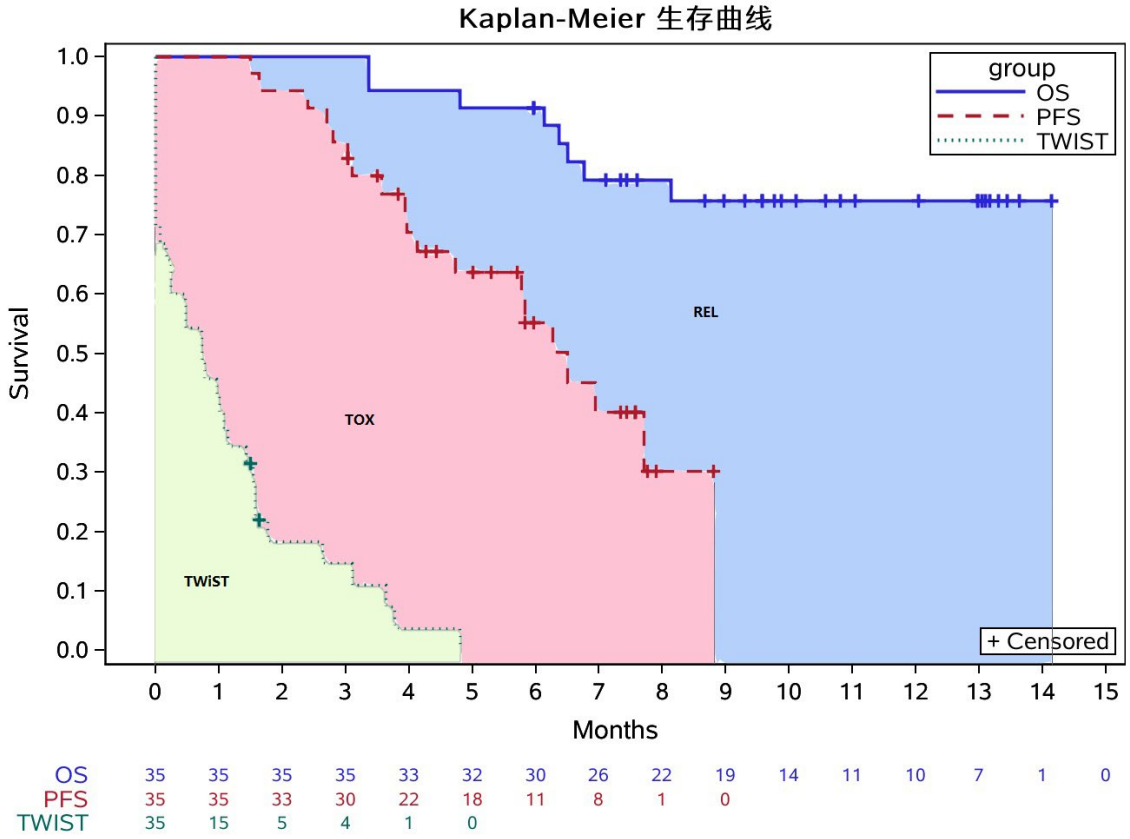
Methods: QoL was assessed using the 30-item core European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) for adults and the European Portuguese self-report version of the Pediatric Quality of Life Inventory™ Cancer Module (PedsQL™ 3.0 Cancer Module) for children and adolescents respectively at baseline and at weeks 6, 12, 18, 24 and after progression/off-treatment. The primary QoL endpoint was the dynamic change in QoL scale. The effect of Grade 3/4 adverse events on QoL was then analyzed using linear regression models, to find out which was the most important factor affecting QoL. The Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment (Q-TWiST) analysis was used to describe treatment results. Survival time was partitioned into three health states: without toxicity before disease progression, with toxicity before disease progression, and disease progression until death.

Results: Compliance with HRQoL assessments was good, ranging from 77.78% of off-treatment/progression to 100% at baseline or other periods. Differences in scores on the EORTC QLQ-C30 global health status (GHS) and all the specific functioning before, during and after treatment were not significantly different with time and did not exceed the predetermined, minimal clinically important difference of 10 points (P=0.14; maximum difference, 4.90 points). During treatment a tendency of improving QoL could be noticed with alleviation of tumor burden whereas after progression a deterioration of QoL would appear. The Intraclass correlation efficient, ICC of PedsQL™ 3.0 Cancer Module showed good to excellent correlation between child self- and parent proxy-reports (range, 0.636-0.908). Like adults, we did not notice any deterioration of QoL during treatment except for progression. Among the descriptive subscales, no reported significantly worse symptom was noticed. The most common adverse events (AEs) were neutropenia (12.08%), leukopenia (16.61%), anemia (12.72%) and diarrhea (4.93%), of which we found that for adults leukopenia might deteriorate GHS (p=0.015), physical functioning (p=0.046) and diarrhea might deteriorate cognitive functioning (p=0.042), while for children diarrhea lowered the scores of pain and hurt (p=0.013), perceived physical appearance (p=0.011) and leukopenia would increase procedural anxiety (p=0.014). Results across the trial analyses showed that the median time without toxicity before disease progression was 0.73 (IQR, 0-1.57) months while the median time with toxicity before disease progression was 3.9 (IQR, 2.3,6.1).

Conclusion: QoL had a trend for improvement in accordance with high objective response in this trial with the receipt of combination therapy of anlotinib and irinotecan for advanced Ewing sarcoma. The observed progression-free survival without impairment of QoL was considered as a meaningful result. The toxicity profile of anlotinib and irinotecan was reflected in the patients' self-reported symptoms but did not translate into significantly worse overall scores during treatment.


GSH_Score
80
70
60
50
0
10
20
30
time


GSH_Score
75
70
65
60
0
5
10
15
20
25
time


Kaplan-Meier 生存曲线
group
OS
PFS
TWIST
Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
REL
TOX
TWiST
+ Censored
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Months
OS 35 35 35 35 33 32 30 26 22 19 14 11 10 7 1 0
PFS 35 35 33 30 22 18 11 8 1 0
TWIST 35 15 5 4 1 0

Poster #004 3412832

THE CLINICAL IMPLICATIONS OF TUMOR MUTATIONAL BURDEN IN OSTEOSARCOMA

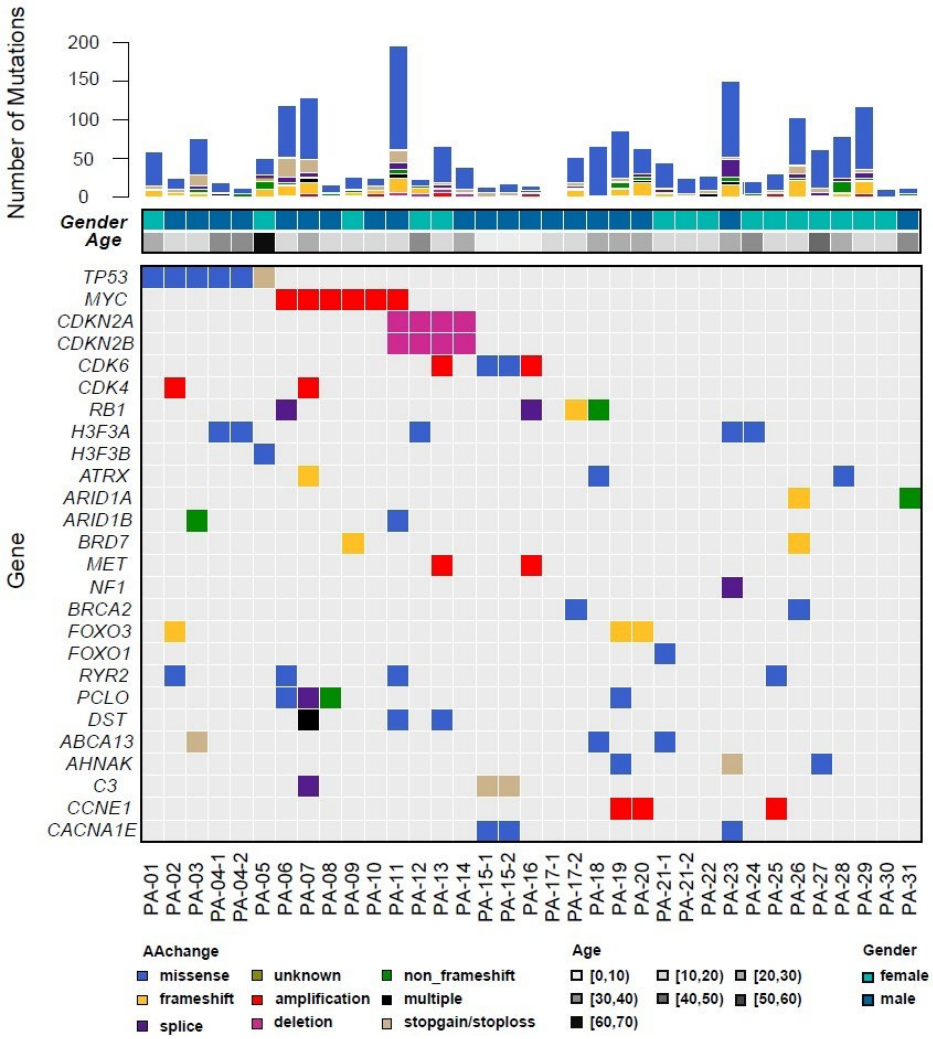
Lu Xie[1], *Yu-Fei Yang*[2], *Wei Guo*[1], *Dongxue Che*[2], *Jie Xu*[1], *Xin Sun*[1], *Kuisheng Liu*[1], *Xiaodong Tang*[1]
[1]*Musculoskeletal Tumor Center, Peking University People's Hospital, Beijing, Beijing, CHINA;* [2]*Genetronhealth. Co. Ltd., Beijing, CHINA*

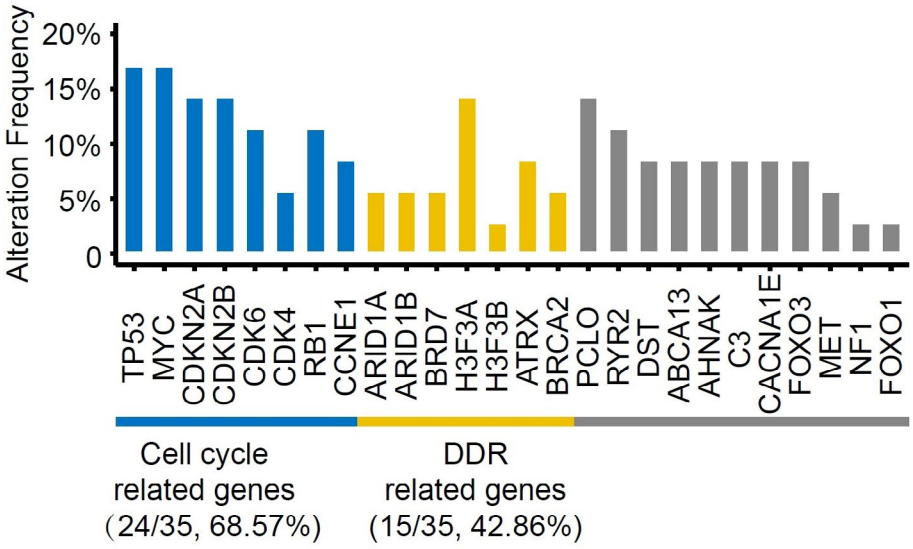
Objective: Tumor cells with high tumor mutation burden (TMB) linked with providing high amount of neoantigen during chemotherapy are strong immunogenic and supposed to trigger strong antitumor immunity, thus predicting clinical outcomes of chemotherapy. However, prognostic impact of TMB is not yet fully understood. In this study, we investigated the clinical implications of TMB in osteosarcoma (OTS).

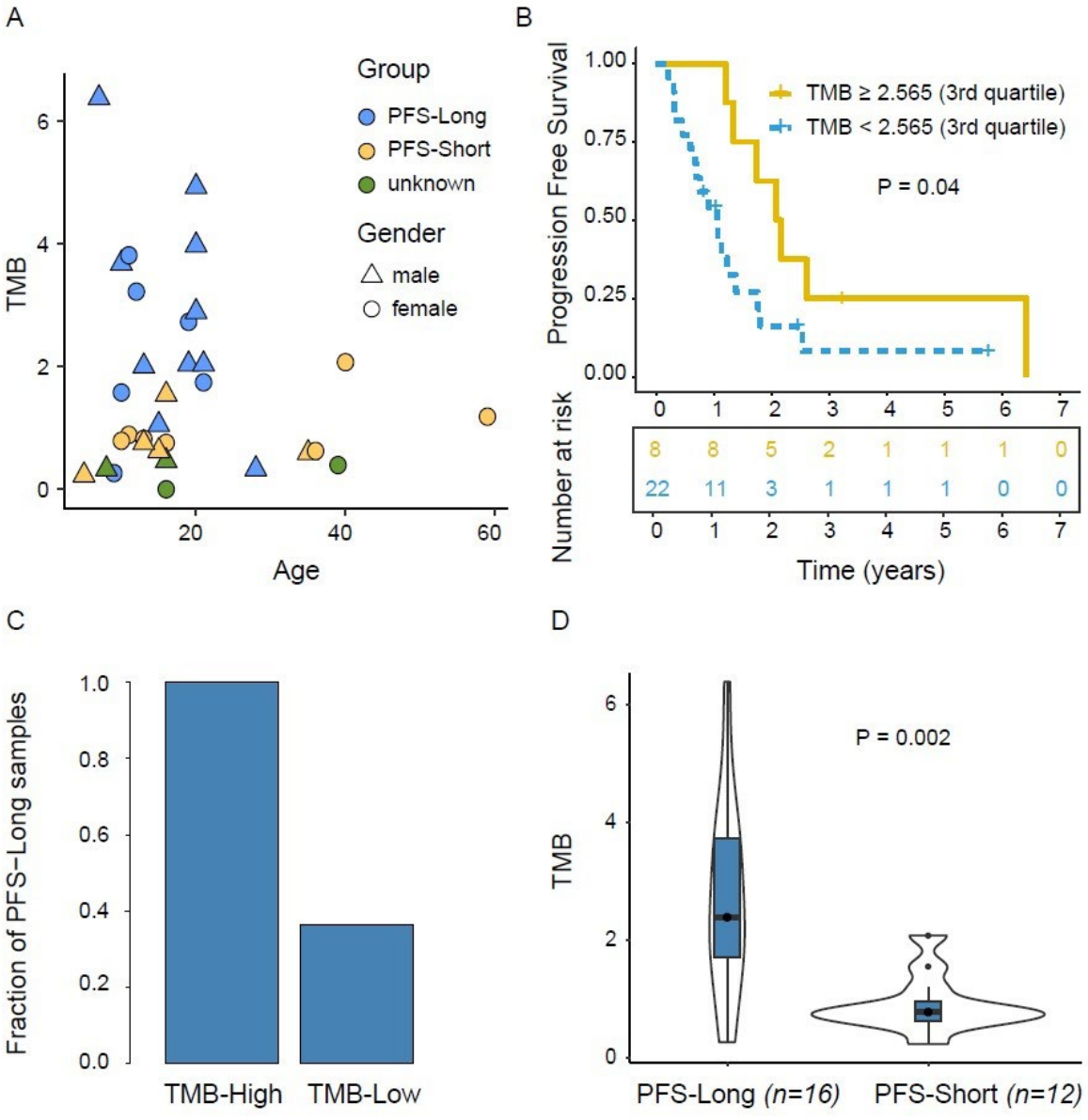
Methods: Genomic profiling was performed on 35 samples from 31 patients with initially treated OTS using whole-exome sequencing (WES). TMB and genomic alterations were evaluated for the associations with clinical outcomes. TMB-High was defined as larger than the third quartile (2.565) and TMB-Low <2.565. Progression-free survival (PFS) was stratified into PFS-Long defined as 400 days and PFS-Short <400 days.

Results: Genes with mutations were mainly involved in cell cycle and DNA damage response and repair. The median PFS was 775.5 days in TMB-High versus 351 days in TMB-Low. The median OS was 1307 days in TMB-High versus 672.5 days in TMB-Low. All patients with TMB-High are PFS-Long, while 36.4% of all patients with TMB-Low were PFS-Long (P=0.003). TMB is significantly greater in PFS-Long than in PFS-Short (P=0.002). Moreover, TMB-High was positively associated with improved PFS (P=0.04, HR=2.62, 95% confidence interval [CI]: 1.01-6.76) and overall survival (OS) (P=0.03, HR=7.40, 95% CI: 0.89-61.56). Furthermore, both univariate and multivariate analyses demonstrated that TMB-Low is significantly associated with worse PFS and OS.

Conclusion: High TMB was independently associated with improved PFS and OS in patients with OTS. Our study demonstrates that TMB may be helpful in combination with traditional clinicopathologic risk factors to optimize risk stratification and guide treatment decisions.




Alteration Frequency
20%
15%
10%
5%
0
TP53
MYC
CDKN2A
CDKN2B
CDK6
CDK4
RB1
CCNE1
ARID1A
ARID1B
BRD7
H3F3A
H3F3B
ATRX
BRCA2
PCLO
RYR2
DST
ABCA13
AHNAK
C3
CACNA1E
FOXO3
MET
NF1
FOXO1
Cell cycle related genes (24/35, 68.57%)
DDR related genes (15/35, 42.86%)


A
Group
PFS-Long
PFS-Short
unknown
Gender
male
female
TMB
Age
B
Progression Free Survival
TMB ≥ 2.565 (3rd quartile)
TMB < 2.565 (3rd quartile)
P = 0.04
Number at risk
Time (years)
C
Fraction of PFS−Long samples
TMB-High
TMB-Low
D
TMB
P = 0.002
PFS-Long (n=16)
PFS-Short (n=12)

Poster #005 3413225

EXTRASKELETAL MYXOID CHONDROSARCOMA: A HIGH INCIDENCE OF METASTATIC DISEASE TO LYMPH NODES

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[1]Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota, UNITED STATES; [2]School of Medicine, Mayo Clinic, Rochester, Minnesota, UNITED STATES; [3]Radiology, Mayo Clinic, Rochester, Minnesota, UNITED STATES

Objective: Extraskeletal myxoid chondrosarcomas (ESMC) are a rare type of soft-tissue sarcoma with limited series reporting outcome of treatment. In soft tissue sarcomas, metastatic disease to lymph nodes is rare; however case reports have noted metastatic disease to lymph nodes in ESMC. Currently there is limited data on the incidence of lymph node spread in ESMC and how this affects patient outcome. The purpose of this study was to assess the outcome of patients with ESMC and determine if lymph node involvment leads to a worse outcome.

Methods: We retrospectively reviewed 30 (21 males, 9 females) patients, mean age 50±16 years, with ESMC of the trunk and extremities. The tumors were located in the lower extremity (n=23, 77%), upper extremity (n= 4, 13%) and chest wall (n=3, 10%). The mean tumor size and volume were 9±5 cm and 490±833cm^3. Tumor grade included high (n=6, 20%), intermediate (n=11, 37%) and low (n=13, 43%). Margins were reported as negative in 27 (90%), in 3 (10%) patients they were microscopically positive (R1). 22 resections were of primary tumors, while 8 were re-excisions of an inavertedly excised sarcoma. Mean follow up was 7±4 years.

Results: Six (20%) patients either presented (n=3, 10%) or developed (n=3, 10%) lymph node metastatic disease over the course of the study. All patients with lymph node metastatic disease had tumors located in the lower extremity (p=0.31). There was no difference in the mean tumor size (12±3 vs. 8±5 cm, p=0.12) or volume (578±425 vs. 464±928 cm^3, p=0.79) in patients with lymph node metastatic disease and those without. Additional risk factors for metastatic disease included larger tumor size (>9 cm, HR 4.36, p=0.01) and local tumor recurrence (HR 3.28, p=0.02). Patients with lymph node metastatic disease underwent resection (n=5) or definitive radiotherapy (n=1).

The 5- and 10-year disease specific survival of 80% and 57%. When comparing patients without, with lymph node metastatic disease and metastatic disease elsewhere, patients with lymph nodes metastatic disease had worse survival than those without metastatic disease, however better 10-year disease specific survival than those with metastatic disease elsewhere (100% vs. 62% vs. 0%).

Local tumor recurrence occurred in 8 patients; with a 5- and 10-year local recurrence free survival of 89% and 52%. A previous inavertedly excised sarcoma was not associated with local tumor recurrence (HR 0.94, 95% CI 0.19-4.69, p=0.94). However a positive surgical margin was associated with local recurrence (HR 11.86, 95% CI 1.67-84.25, p=0.01).

Following resection, complications occurred in 9 (30%) patients, most commonly due to a wound complication (n=6, 20%). At the last follow-up, the mean MSTS93 was 79±21%.

Conclusion: The results of this study highlight the high incidence of lymph node metastatic disease in patients with extraskeletal myxoid chondrosarcoma. Although survival in these patients is worse survival compared to those without metastatic disease, their survival is better than those with metastatic disease elsewhere. Due to the high incidence of lymph node metastatic disease, staging these patients with studies which examine the lymph node basin are important, especially for those with lower extremity tumors.

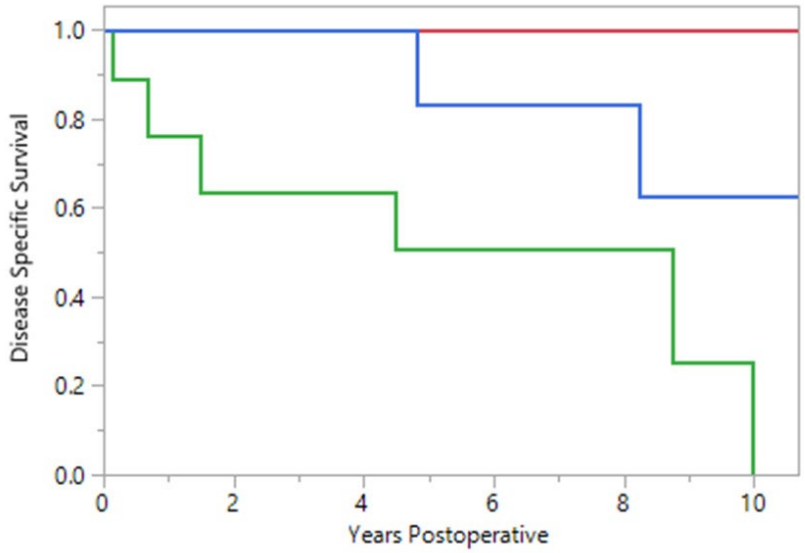

Figure: Following surgical resection, the 5- and 10-year, patients with lymph node metastatic disease (83% and 62%, blue) had worse disease specific survival for patients without metastatic disease (100% and 100%, red), but better survival compared to those with metastatic disease elsewhere (50% and 0%, green).

Poster #006 3420516

CLINICAL EXPERIENCE OF 6 CASES OF MYXOID PLEOMORPHIC LIPOSARCOMA

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[1]*National Cancer Center Japan, Chu-ou-ku, Tokyo, JAPAN*

Objective: Myxoid pleomorphic liposarcoma (MPL) is a rare disease that occurs in young people and was reported by Alaggio et al. in 2009 as a poor prognosis liposarcoma.

Methods: Six patients diagnosed with MPL in our hospital are reviewed and reported with a discussion of the literature. There were two males and four females, aged between 17 and 39 years (mean age: 22.8 years).

Results: The primary site was mediastinum in three cases, supraclavian, retroperitoneal, and lower limbs in one case each. The average tumor size at the time of primary presentation was 9.3 cm, and all cases showed a trend of rapid growth. Except for unresectable cases, resection was performed in five cases (R0: 2 cases, R2: 3 cases). One patient with mediastinal MPL had an R0 resection, developed lung metastases 4 years after surgery, and underwent additional resection. The mean time to recurrence or metastasis after resection was 22.8 months, and the outcome at the final follow-up was 1 CDF (6 years postoperatively), 1 NED (7 years postoperatively), and 4 DODs.

Conclusion: There have been 18 cases of MPL in the past, with a median age of onset of 17 years and a high incidence in the mediastinum. A complication of Lifuraumeni syndrome has also been reported. According to the past reports, the prognosis is extremely poor because lung metastasis rate of 40% or more and 70% die within 36 weeks after diagnosis, Histopathologically, it is similar to myxoid liposarcoma, but it has been reported that the FUS-DDIT3 or EWSR-DDUT3 fusion gene is not rearranged. In addition, it is known that no amplification of the MDM2 gene is detected by the FISH. The precise classification and terminology of this liposarcoma has recently been included in the new edition of the WHO Classification of Soft Tissue and Bone Tumors. We should consider the possibility of MPL in young patients with mucous-type liposarcoma without fusion gene. It is essential to establish accurate diagnosis and treatment methods in the future.

Poster #007 3425027

VERSICAN AND EXTRACELLULAR MATRIX REMODELING PROMOTE CIRCULATING OSTEOSARCOMA CELL EXTRAVASATION AND METASTATIC SEEDING

Mark M. Cullen[1], *Tyler A. Allen*[2], *Lan Nguyen*[3], *Hiroyuki Mochizuk*[6], *Paige Nemec*[6], *Etienne M. Flamant*[1], *Sarah Hoskinson*[4], *Beatrice Thomas*[2], *Suzanne B. DeWitt*[4], *Kathryn E. Ware*[2], *Luke Borst*[6], *Ke Cheng*[6], *William C. Eward*[5], *Jason A. Somarelli*[2]

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Objective: Osteosarcoma (OS) is the most common primary bone tumor, and the 5-year survival for patients who present with metastatic disease is 30%. For metastatic OS patients, it is critical to identify the molecular mechanisms and pinpoint new therapeutic interventions to prevent metastatic spread.

Methods: Circulating tumor cells were generated by injecting fluorescently-labeled D17 and HMPOS canine OS cells into the vasculature of embryonic zebrafish (48 hours post fertilization) and isolating extravasated cells (Figure 1). Cells that subsequently extravasated from the zebrafish vasculature were collected, expanded in culture, and characterized using RNA-Sequencing (RNA-Seq). Pathway enrichments were identified using Gene Set Enrichment Analysis (GSEA). The prognostic relevance for specific genes and pathways was assessed using the R2 Genomics Platform. Knockdown studies were performed on human OS 143B cells using siRNAs, and scratch wound assays were used to quantify the impact of knockdown on cellular migration.

Results: Using a zebrafish metastasis model, we isolated tumor cell clusters that had extravasated from the vasculature into the surrounding tissues. RNA-Seq analysis of these extravasated cells pinpointed a number of potential pathways of relevance, including E2F, Myc, and extracellular matrix (ECM) remodeling pathways. Analysis of gene interaction networks within the ECM pathway revealed versican (*VCAN*) as a commonly upregulated gene in metastatic OS cells in both cell lines analyzed. Consistent with a role in invasion/metastasis, knockdown of *VCAN* significantly inhibited OS cell migration in human 143B cells (Figure 2).

Conclusion: Using a novel zebrafish model of metastasis we were able to capture clusters of extravasating circulating OS cells for downstream profiling. These efforts identified *VCAN* and the ECM remodeling pathway as key modulators of extravasation. Preliminary results suggest *VCAN* could be a future pharmaceutical target of interest to reduce OS extravasation and prevent metastatic colonization.

Figure 1: Dog osteosarcoma cells being injected into our zebrafish model. Extravasated cells were collected and grown in culture.

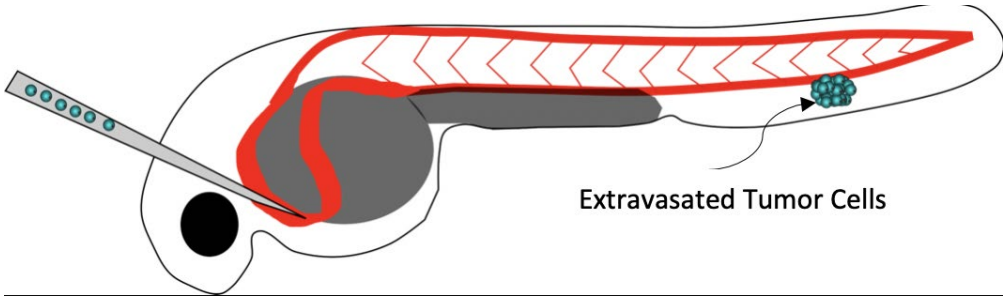
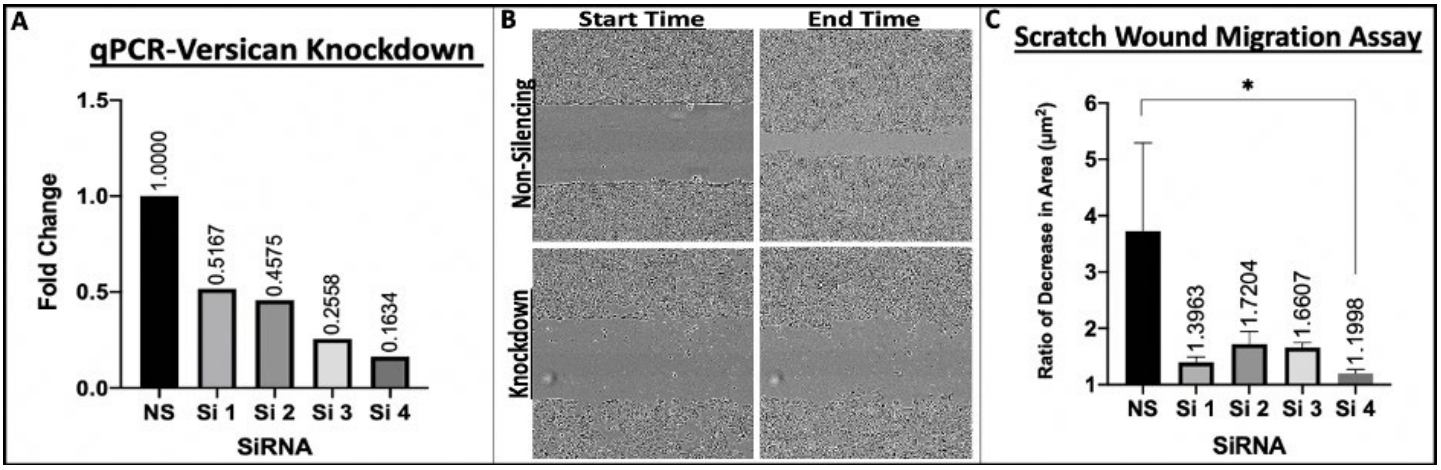


Figure 2: A) qPCR demonstrating *VCAN* knockdown in 143B osteosarcoma cells. B) Photo of scratch wound assay providing a visual representation of the difference in migration between the control condition (non-silencing) and the knockdown condition. C) Scratch wound migration assay showing that all siRNAs inhibited migration of cells when compared to the control condition.



Poster #008 3427115

THE ANATOMIC DISTRIBUTION OF OSTEOSARCOMA

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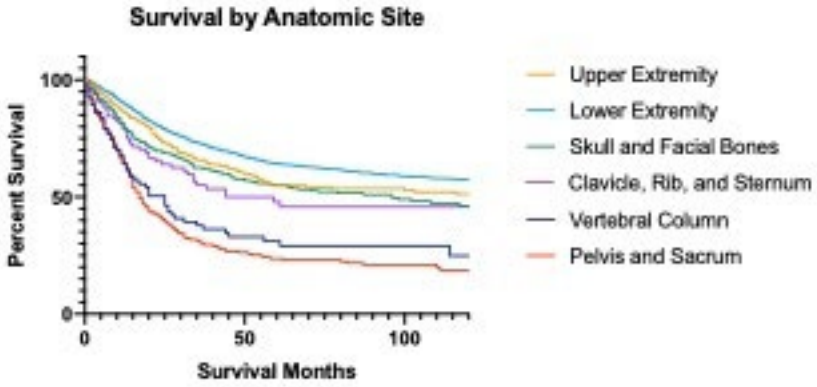
Objective: Osteosarcoma (OS) is the most common malignant sarcoma of bone and is known to manifest most frequently as a primary tumor of the distal femur, proximal tibia, or proximal humerus. Comparatively less is known regarding the epidemiology and survival of uncommon primary tumor locations, including bones of the face and skull, vertebral column, thorax, and pelvis. In this study the epidemiology and survival of OS is compared across anatomic sites.

Methods: The Surveillance, Epidemiology, and End Results (SEER) program was queried for primary OS of the bony pelvis from 2004-2017. Frequency and survival characteristics were compared across anatomic locations of the primary tumor, categorized as tumors of the lower extremities (LE), upper extremities (UE), skull and facial bones, vertebral column, pelvis and sacrum, or bones of the thoracic cage including the rib, clavicle, and sternum. Cases with Collaborative Stage variables (available 2004+) were analyzed by grade, histological subtype, surgical intervention, tumor size, tumor extension, and presence of metastases at diagnosis. Kaplan-Meier and log-rank tests were performed to assess survival. These database findings were compared to relevant OS literature.

Results: In total 3923 cases of OS were reviewed from years 2004-2017. Of surveyed tumors, 54.96% (n=2156) originated in the LE, 10.83% (n=425) in the UE, 9.56% (n=375) in the skull or facial bones, 9.23% (n=362) in the pelvis or sacrum, 2.73% (n=107) in the ribs, sternum, or clavicle, and 2.42% (n=95) in the vertebral column. The 5-year survival for all cases was 58.9% (n=3350), compared to a 5-year survival of 65.5% (n=2029) for tumors in the LE, 57.5% (n=389) in the UE, 61.9% (n=79) in the skull or facial bones, 26.7% (n=250) in the pelvis or sacrum, 58.9% (n=72) in the ribs, sternum, or clavicle, and 33.3% (n=76) in the vertebral column.

Conclusion: SEER database review indicates OS manifests most frequently in long bones of the lower extremity, followed by long bones of the upper extremity, skull and facial bones, pelvis and sacrum, bones of the thoracic cage, and the vertebral column least frequently. Primary tumors of the LE, UE, skull and facial bones, and thoracic cage have superior prognosis compared to tumors of the vertebral column and pelvis. This study further corroborates epidemiological characteristics of OS and provides prognostic guidance specific to the anatomic location of the primary tumor.



Poster #009 3428769

PROGNOSIS OF PATIENTS WITH METASTATIC SOFT TISSUE SARCOMA: ADVANCES IN RECENT YEARS

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Objective: The objective of this study was to investigate the prognosis of patients with metastatic soft tissue sarcoma (STS) and to define prognostic indicators for overall survival (OS).

Methods: All patients who were treated at the Sarcoma Unit at the Mannheim University Medical Center, Mannheim, Germany, between 2010 and 2016 and developed metastatic disease deriving from a STS were included in this retrospective analysis. OS was investigated using data from clinical records and German registry offices. Clinical and pathological characteristics were recorded and analyzed.

Results: A total number of 212 patients developed metastatic disease from STS during that period. Median OS after first documentation of metastatic disease was 24 months (Confidence Interval [CI] 95 %, 21 - 33). 1-year, 2-year and 5-year OS rates were 70.0 % (CI 95 %, 64 % - 77 %), 49.9 % (CI 95 %, 43 % - 58 %) and 24.8 % (CI 95 %, 19 % - 33 %), respectively. In multivariate analysis, significant predictors for mortality appeared to be male gender ($p = 0.0005$), age > 55 years ($p = 0.003$), location and size of the primary tumor, histology, disease-free-interval and synchronous metastasis ($p = 0.001$).

Conclusion: Being treated in a high-volume reference center for STS in Germany, STS patients with metastatic disease could demonstrate a significantly increased OS compared to former analyses. Drug developments with new active compounds such as pazopanib and trabectedin, multimodality treatment concepts and consistent therapy within a specialized sarcoma reference center are possible explanations for the improvements in survival of these patients. These data can be used as a benchmark for upcoming studies and highlight that further research on treatment strategies in this rare disease is urgently needed.

Poster #010 3434418

RECURRENT MULTIFOCAL PLEOMORPHIC SARCOMA OF THE SCALP RESPONDING TO PEMBROLIZUMAB

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Objective: In Fall 2016, this 75 year old man hit the top of his head with a branch and the area just wouldn't heal. He underwent biopsy of this superior scalp lesion 10/19/2016 which was called "leiomyosarcoma" at the time. The lesion was estimated to measure approximately 2 cm in diameter. Mohs resection was performed 01/19/2017.

Local recurrence in March 2017 necessitated a second, wider resection 03/30/2017, requiring a skin graft for closure. Surgical defect was 4.5 x 4.3 cm. Path reports threw out the idea of an undifferentiated pleomorphic sarcoma this time. In the adjuvant setting he received radiation therapy to the operative site, 6600 cGy in 33 fractions, July 2017.

By Summer 2018, while getting a haircut, a 1 cm nodule on the right frontoparietal scalp was noticed. This lesion was 2 inches lateral to the prior radiation field. Biopsy on 08/14/2018 was read as undifferentiated pleomorphic sarcoma. Staging CT head/neck/chest 09/07/2018 revealed no evidence of metastatic disease. On 09/24/2018, he underwent revision of the previous operative site, local flap reconstruction with tissue transfer/rearrangement and craniectomy. The main surgical specimen contained the main 1.5 x 0.6 cm focus of poorly differentiated sarcoma, with multiple subcutaneous satellite lesions. Satellite metastases were within 1 mm of the lateral margin and 1.5 mm from the deep margin. There was no evidence of lymphovascular invasion.

Baseline PET 10/26/18 showed increased FDG uptake about the right scalp resection site, likely post therapeutic, but no other evidence of metastatic disease. He underwent reirradiation, 60Gy in 30Fxs, completing on 2/26/2019. This area has never healed since re-irradiation.

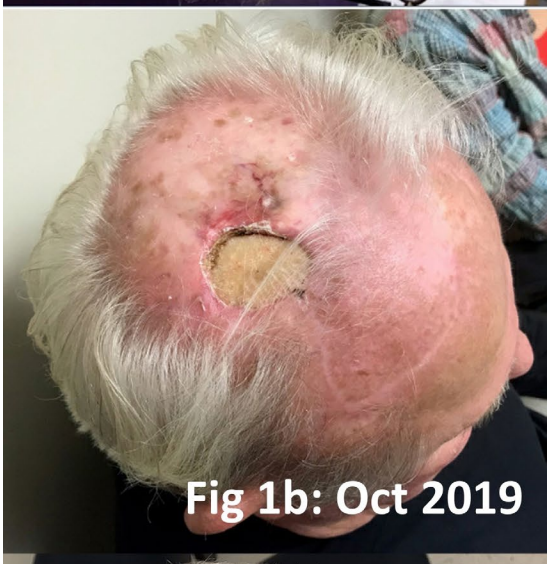
Over Spring 2019, him and his wife noticed at least two growing nodularities. No redness, warmth, fluctuation or drainage to suggest infection. Repeat staging scans done June 2019 showed recurrent nodularity in L frontal and R posterior scalp areas, but no locoregional nodes or distant metastases. He saw his dermatologist 6/11/19, who biopsied five separate areas on scalp - all five areas were c/w recurrent poorly-diff UPS (Fig 1a). At this time, we went back and looked at PDL-1 expression of the tumor removed from the previous September surgery, using immunohistochemistry using DAKO PD-L1 IHC 22C3 pharmDX. It was noted to be high at 90-100%. (Fig 2)

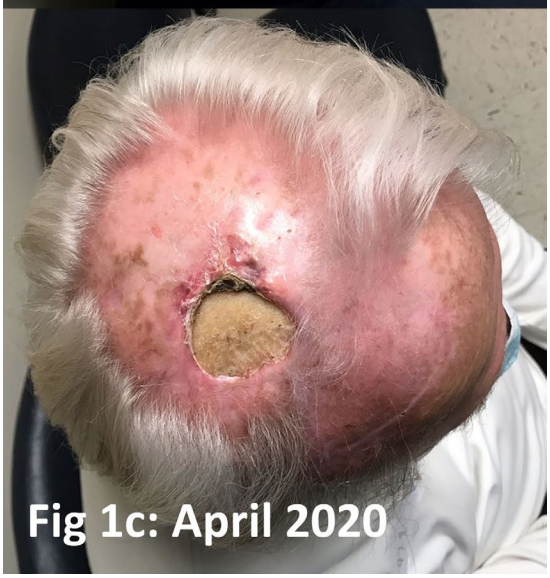
Methods: Because of the multifocal recurrence on scalp refractory to multiple surgeries and two separate courses of radiation, we started off-label use of pembrolizumab early July 2019, as opposed to a large free tissue flap/reconstruction.

Results: Within the first couple months, he could tell the nodules were responding (Fig 1b). He has remained on pembrolizumab since, still showing no signs of local recurrence or distant metastases (Fig 1c). He has tolerated immunotherapy well.

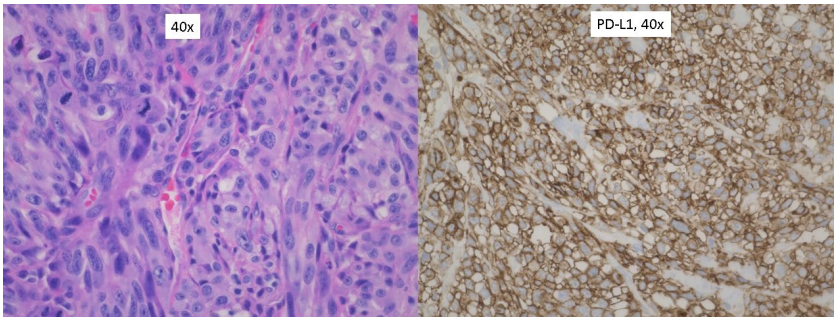
Conclusion: We report a case of recurrent, multifocal, PDL-1-overexpressed pleomorphic sarcoma of scalp responsive to off-label pembrolizumab. We plan to stop after 1 year (like in adjuvant melanoma therapy), then get back into surveillance mode. We would encourage others to look at immunotherapy as a systemic option for recurrent/refractory undifferentiated pleomorphic sarcoma of the scalp, especially in those with overexpressed PDL-1 via immunohistochemistry.

Biopsy locations of the five separate areas showing recurrent undifferentiated pleomorphic sarcoma of the scalp (Fig 1a). Within a couple months, complete response was seen on scalp (Fig 1b) that has been maintained to date (Fig 1c)





Pathology specimen showing undifferentiated pleomorphic sarcoma of the scalp (left, 40x magnification), with PDL-1 expression tested by immunohistochemistry using DAKO PD-L1 IHC 22C3 pharmDX (right, 40x magnification).



Poster #011 3434659

PROGNOSTIC FACTORS OF HIGH-GRADE OSTEOSARCOMA: ANALYSIS OF 20 YEARS DATA AT A SINGLE CENTER IN JAPAN

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Objective: High-grade osteosarcoma is a malignant bone tumor and many trials have been conducted seeking its optimal treatment. The purpose of this study was to assess the prognostic factors and outcomes of patients with high-grade osteosarcoma who underwent the primary surgery in our institute.

Methods: This retrospective study was carried out on 50 patients who were diagnosed as primary high-grade osteosarcoma without metastases and underwent radical wide resection in our institute from 1998 to 2018. Data obtained from patients' medical records included patients' sex, age group (≧40 or <40), primary tumor size (≧10cm or <10cm), site of tumor (extremity or trunk), surgical margins (adequate or inadequate), pathological margins (microscopic negative (R0) or microscopic positive (R1)), and chemotherapy response grade (good (Grade2,3) or poor (Grade 0,1)). Over-all, recurrence-free, and postoperative metastasis-free survival were calculated using the Kaplan-Meier method and compared by the log-rank test and the Cox proportional hazard regression method. The values of $P<0.05$ were considered statistically significant.

Results: Fifty patients in total including 30 males (60%) and 20 females (40%) were examined. The patients' ages varied from 11 to 76 years old with the mean age of 27. As for the age groups, 10 patients were ≧40 and 40 patients were <40. The median follow-up was 66 months (varying from 2 to 199 months). Forty-two patients (84%) underwent limb salvage surgery, while the rest 8 patients underwent amputations. As for the size of tumor, the major axis was ≧10cm in 36 patients and <10cm in 14 patients. The tumors were found in extremities for 46 patients and in trunks for 4 patients. The evaluation of surgical margins were wide for 40 patients, marginal for 8 patients, and intralesional for 2 patients. Pathological margins were evaluated as R0 for 48 patients and R1 for the rest 2 patients. The 5-year over-all survival rate was 60.3% (95% confidence interval (CI), 0.449-0.727). The 5-year recurrence-free survival rate was 54.3% (95% CI, 0.391-0.672). The 5-year metastasis-free survival rate was 51.0% (95% CI, 0.362-0.640). In log-rank test, the bigger tumor size (≧10cm)was associated with the worse metastasis-free survival rate ($p<0.05$). On the other hand, R1 margins correlated with the worse overall and recurrence-free survival ($p<0.05$). Univariate analyses also suggested significant correlations between R1 and worse prognosis in the 5-year over-all as well as in the recurrence-free survival ($p<0.05$). In multivariate analyses, no significant difference was found in the factors examined for all the survivals.

Conclusion: The retrospective review on clinical outcomes of high-grade osteosarcoma in a single center for 20 years reaffirmed already-known prognostic factors including pathological margins. Among the evaluated factors showing significant difference for prognosis, more surgical efforts should be made on ensuring appropriate pathological margins wide enough to realize better results in over-all survival rate as well as in recurrence-free survival rate.

Poster #012 3436390

CHARACTERISTICS AND OUTCOMES OF LOCALLY RECURRENT RETROPERITONEAL SARCOMA AFTER FIRST RELAPSE IN A SINGLE TERTIARY ASIAN CENTRE AND APPLICABILITY OF THE SARCULATOR

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Objective: Retroperitoneal sarcomas (RPS) account for approximately 15% of soft tissue sarcomas where five-year overall survival rate is approximately 50% and locoregional recurrences are observed in 40% to 50% of the patients within the first five years following surgery. Various factors have been shown to influence survival outcomes, such as histological subtype and tumour size. A nomogram for first relapse locally recurrent RPS was developed using 602 patients from 22 centres. The recurrent RPS *Sarculator* is available in an electronic interface and includes variables of age, size, margins of re-resection, radiotherapy, chemotherapy and histology to predict for 6-year disease-free survival (DFS) and overall survival (OS). It has not been validated externally. This study aims to validate the *Sarculator* recurrence nomogram in predicting the survival outcomes of recurrent RPS patients in an Asian population as well as examine relapse patterns.

Methods: Patients diagnosed with first recurrent RPS from 1 January 2000 to 31 December 2017 with first local relapse and eligible for curative re-resection were retrospectively analysed. Extent of surgery was individualised and recommendations of adjuvant therapy were based on international standards. Patients were reviewed post-resection every 3 to 4 months for the first 2 to 3 years and 6-monthly to annually thereafter. R0/ R1 margin is considered as complete resection, including microscopically negative margin (R0) and microscopically positive but macroscopically clear margin (R1). R2 is defined as incomplete resection with residual disease or tumour rupture. Harrell's C concordance index was used to determine the nomogram's discriminative ability and calibration plots were used to assess accuracy. For the calibration, the patients were divided into 3 groups. Death data was retrieved from the National Birth and Death registry for accuracy.

Results: There were 53 patients included in this study. Patient and tumour characteristics have been summarised in Table 1. All patients had their second resection at a single centre. 66.0% had their first resection at the same centre. The median age was 53 (range 21- 79) at diagnosis, median tumour size was 17cm (12cm to 28cm) and median follow-up duration was 44.1 months. Most common subtypes were de-differentiated liposarcoma (DDLPS) (56.6%), well-differentiated liposarcoma (WDLPS) (20.8%) and leiomyosarcoma (LMS) (11.3%) with a majority being high-grade (75.5%). The median disease-free interval was 2.9 years (2- 5.3 years) from the first surgery. The median age at second surgery was 56 (21- 79) and all patients had a complete resection (R0/ R1). Recurrence patterns differed with subtypes where 90.9% and 9.1% of WDLS, 76.7% and 16.7% of DDLPS and 83.3% and 16.7% of LMS had local and distant relapses respectively from the second surgery. 62.5% of distant relapses was in the lung followed by nodes (18.8%) and liver (12.5%). The 5-year OS from the second surgery was 66.2% (95% CI: 54.3%- 80.8%). The 1-year, 3 years and 6 years DFS were 50.2% (95% CI: 38.2% - 65.9%), 10.4% (4.26% - 25.5%) and 3.91% (0.684% - 22.4%) respectively. Overall, 32 patients (60.4%) had passed away from sarcoma. The concordance indices for 6-year OS and DFS were 0.7 and 0.65 (Figure 1) respectively which represents a fairly accurate prediction by *Sarculator*.

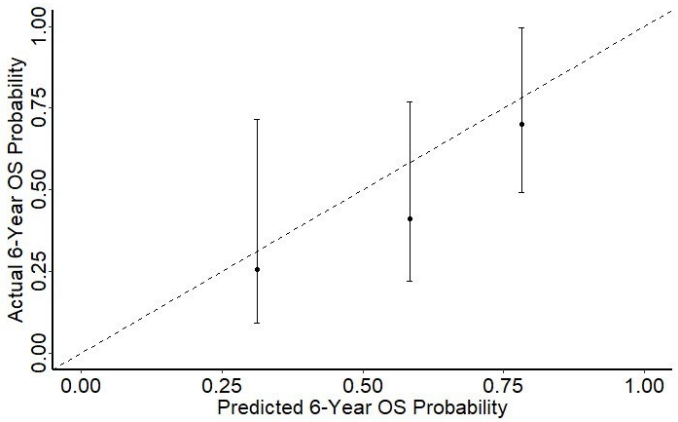
Conclusion: Our study has shown the *Sarculator* nomogram for primary recurrent was applicable in our cohort and its potential application in an Asian setting. The *Sarculator* nomogram will be a useful tool in clinical practice to strengthen the prognosis-based decision making and enhance risk stratification. Moving forward, novel therapies are needed to improve the prognosis of recurrent RPS.

TABLE: Patient and tumour characteristics

Variable		n (%)
Median age at diagnosis (range) (n = 53)		53 (21-79)
Median size of primary tumor (interquartile range) (n = 53)		17 [12-28]
Histology (n = 53)	DDLPS	30 (56.6%)
	WDLPS	11 (20.8%)
	LMS	6 (11.3%)
	SFT	2 (3.8%)
	MPNST	1 (1.9%)
	Others	3 (5.7%)
Grade (n = 53)	1	13 (24.5%)
	2	22 (41.5%)
	3	18 (34%)
Number of resected organs at first surgery (n = 53)	0	20 (37.7%)
	1	21 (39.6%)
	2	9 (17%)
	3	2 (3.8%)
	4	1 (1.9%)
Chemotherapy for primary tumour (n = 53)	No	52 (98.1%)
	Yes	1 (1.9%)
Radiotherapy for primary tumour (n = 53)	No	46 (86.8%)
	Yes	7 (13.2%)
Multifocality at second surgery (n = 53)	No	27 (50.9%)
	Yes	26 (49.1%)
Margins (n = 53)	R0	13 (24.5%)
	R1	40 (75.5%)
Median DFI from first surgery in year (IQR) (n = 53)		2.9 (2 – 5)
Local recurrence from second surgery (n = 53)	No	10 (18.9%)
	Yes	43 (81.1%)
Distant recurrence form second surgery (n=53)	No	37 (69.8%)
	Yes	16 (30.2%)

De-differentiated liposarcoma (DDLPS) (56.6%); well-differentiated liposarcoma (WDLPS); leiomyosarcoma (LMS); solitary fibrous tumour (SFT); malignant peripheral nerve sheath tumour (MPNST); disease-free interval (DFI)

Figure 1: Calibration plot showing 6-year OS against predicted probabilities



Poster #013 3436645

CURRICULUM-BASED ONLINE CME IMPROVES PHYSICIAN KNOWLEDGE OF EPITHELIOID SARCOMA

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Objective: Soft tissue sarcomas (STS) are rare malignancies of mesenchymal origin with more than 50 histological subtypes. Epithelioid sarcoma (ES) is an uncommon subtype of STS, characterized by a loss of the INI1 protein. ES can manifest either as classic or proximal and accurately diagnosing ES is challenging. The prognosis is typically poor for metastatic ES and optimal treatment remains undefined. Recently, there have been advances beyond surgical resection and chemotherapy, including targeted therapy. Due to the rarity of ES and lack of defined treatment options, clinicians are challenged to stay current with emerging data and how best to integrate new agents into multidisciplinary treatment paradigms. The objective of this study was to assess changes in oncologists' and pathologists' knowledge, competence, and confidence through participation in education regarding ES treatment options.

Methods: A series of two online educational activities were launched in 2019-2020 covering gaps regarding emerging therapies for epithelioid sarcoma and how to individualize treatment. One activity included a three-part, three faculty, text-based activity overviewing various perspectives on the diagnosis and management of ES. The other activity included a 15-minute, two faculty, video discussion overviewing emerging management options within ES. Educational effect was assessed with a repeated pairs pre-/post-assessment study with a 3-item, multiple choice, knowledge and decision-making questionnaire and one confidence assessment question. For all questions, each participant served as his/her own control. Pre- and post-assessment scores were compared to determine relative changes in the proportion of correct responses. Data were aggregated across the two different activities in order to examine impact. A McNemar's test assessed statistical significance at the $P < 0.05$ level.

Results: Oncologist and pathologist learners had a measurable increase in their confidence regarding epithelioid sarcoma management post-education (64% and 40%, respectively). The learning objectives were grouped under four themes. Significant improvements in knowledge and competence were observed for both oncologists and pathologists post-education (Table 1 and 2).

Conclusion: This study demonstrated that participation in an online CME curriculum consisting of video discussion and text-based formats resulted in statistically significant improvements in knowledge and competence of oncologists and pathologists. As data and available therapies emerge, new educational activities are paramount to reinforce knowledge, address residual gaps, and further increase clinicians' confidence in the management of ES.

Table 1 - Oncologists

Oncologists					
Theme	Analysis (N)	Pre %	Post %	% Improvement	P Value
Knowledge of Surgical Management	160	78%	89%	14%	<.001
Knowledge of Mechanism of Action	50	54%	76%	41%	<.01
Knowledge of Molecular Characteristics	160	51%	88%	73%	<.001
Competence in Incorporating Therapies	160	33%	78%	136%	<.001

Table 2 - Pathologists

Pathologists					
Theme	Analysis (N)	Pre %	Post %	% Improvement	P Value
Knowledge of Surgical Management	87	49%	69%	41%	<.01
Knowledge of Mechanism of Action	50	48%	64%	33%	<.01
Knowledge of Molecular Characteristics	87	46%	76%	65%	<.001
Competence in Incorporating Therapies	87	21%	52%	148%	<.001

Poster #014 3436999

ASSOCIATION BETWEEN OCCUPATIONAL EXPOSURES AND SARCOMA INCIDENCE AND MORTALITY: SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: Sarcomas represent a rare, heterogeneous group of over 80 different tumors arising from mesenchymal or connective tissue. In 2019, soft-tissue sarcomas (STS) accounted for approximately 0.8% of all cancers and 0.9% of all cancer deaths in adults in the United States. Due to the complexity and rarity of sarcomas, their etiology remains poorly understood. The objective of the present study was to systematically assess the association between various occupational exposures and risk of sarcomas.

Methods: A systematic literature search using the PubMed, Scopus, EMBASE and Cochrane databases was performed to identify relevant cohort and case-control studies. A meta-analysis method was applied on the incidence and mortality outcomes, 95% confidence interval (CI) was calculated using a random-effects model. Forest plots were generated, displaying the individual study effects and the meta-analysis effect.

Results: A total of 59 publications were included in our study. 15 case-control studies involving 2 128 sarcoma cases and 21 486 controls assessed the association between exposure to phenoxy herbicides and chlorophenols and sarcoma incidence. The pooled odds ratio (OR) was 1.82 (95% CI: 1.17 – 2.84), p = 0.008, indicating significant positive association. 4 cohort studies involving 11 STS cases and 59 289 participants assessed the association between exposure to phenoxy herbicides and chlorophenols and sarcoma mortality. The pooled SMR was 40.93 (95% CI: 2.19 - 765.90), p = 0.013, indicating a statistically significant positive association. However, both cohort and case-control studies were limited by significant heterogeneity across the studies. 4 cohort studies involving 30 797 participants evaluated the association between exposure to dioxins and STS mortality. There were 14 deaths due to STS in these studies. The pooled SMR was 2.56 (95 % CI: 1.60 - 4.10), p = < 0.001, indicating a statistically significant positive association between exposure to dioxins and STS mortality. Excess death due to angiosarcoma of the liver (ASL) and other STS was observed in 3 cohort studies involving 12 816 participants exposed to vinyl chloride monomers (VCM). The pooled risk ratio (RR) for ASL was 19.23 (95% CI: 2.03 - 182.46, p = 0.010); the pooled RR for other STS was 2.23 (95 % CI 1.55 - 3.22, p < 0.001). For exposure to wood dust and woodworking occupation the pooled OR was 2.16 (95% CI: 1.39 - 3.36, p < 0.001), based on 4 case-control studies and 8 593 participants.

Conclusion: Overall, our findings suggest a statistically significant positive association between higher exposure to dioxins and increased mortality from STS; between cumulative exposure to VCM and increased mortality from ASL and other STS; woodworking occupation and exposure to wood dust and sarcoma incidence. Notwithstanding the high heterogeneity of the studies, workers exposed to phenoxy herbicides and chlorophenols may experience an increased incidence of STS based on available case-control studies. However, meta-analysis of cohort studies for exposure to chlorophenols and phenoxy herbicides produced conflicting results. Conducting new large case-control studies and extending follow-up of previously assembled cohort studies would be effective ways at reducing uncertainties and could provide more evidence on other risk factors reported in our study.

Poster #015 3437318

PELVIC SOFT TISSUE SARCOMAS: AN INTERNATIONAL RETROSPECTIVE STUDY FROM THE TRANS-ATLANTIC AUSTRALASIAN RETROPERITONEAL SARCOMA WORKING GROUP (TARPSWG)

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Objective: Pelvic soft tissue sarcomas (PSTS) are usually analyzed with retroperitoneal sarcomas (RPS) as they often share many characteristics, even when limited to the infra-pelvic space. However, PSTS may require different therapeutic options and the standard approach to RPS may not apply. Our objective was to describe patterns of presentations, treatment modalities and outcomes of PSTS treated at TARPSWG centers.

Methods: A retrospective analysis of preliminary data of adult primary localized PSTS treated between 2005 and 2018 in 16 TARPSWG centers was performed. In order to be considered, tumors had to originate from non-visceral pelvic structures, including extension into the abdominal cavity, herniation through the sciatic notch, the obturator foramen and/or inguinal ligament. Gynecological, urogenital, Ewing, pediatric sarcomas and desmoid tumors were excluded. Clinical, histological and treatment characteristics were collected, as well as incidence of local recurrence (LR) and distant metastasis (DM), overall and disease-specific survival (OS, DSS). Survival analysis was performed using Kaplan-Meier plots and log rank test. Competing risk analysis was used to estimate incidence of LR and DM. Multivariate regression analysis was performed to identify prognostic factors.

Results: 270 patients met eligibility criteria, of which 249 (92.2%) underwent surgery. Median age was 56 years (IQR, 47-67); mean size was 13.0 cm (IQR, 8.0-19.0); most common histologies were leiomyosarcoma (LMS, n=64, 25.7%), dedifferentiated liposarcoma (DDLPS, n=49, 19.7%), solitary fibrous tumor (SFT, n=47, 18.9%), well-differentiated liposarcoma (WDLPS, n=29, 11.6%), and others (n=60, 24.1%). Clinicopathological characteristics are described in **Table 1.** Median follow up after surgery was 61 months (IQR, 32-107). Operated patients received (neo-)adjuvant chemotherapy or radiotherapy in 82 (32.9%) and 113 (45.4%) cases respectively. Multimodal treatment significantly differed among histotypes, with preoperative chemotherapy given in 25% of LMS, preoperative radiotherapy in 29.8% of SFT, and postoperative chemotherapy in 11.8% of others PSTS **(Figure 1)**. Surgery was complete (R0/R1) in 210 patients (84.3%). The most frequently resected organs were adnexa (22.9%), rectum (22.5%), psoas muscle (22.1%), iliac vein (18.9%), ureter (15.7%), and bladder (14.9%). Median number of resected organs was 2. Severe complications (Clavien-Dindo grade ≥3) occurred in 49 (19.7%) patients, and a re-operation was needed in 27 (10.8%) leading to a mortality of 3 patients (1.2%). Estimated incidences of 5-year LR and DM were 21.1% (95%CI 15.8-27.3%) and 30.5% (95%CI 24.4-37.0%), respectively. 5-year DSS and OS were 70.0% (95%CI, 62.7-75.4%) and 67.7% (95%CI, 60.8-73.6%), respectively. DSS was significantly different according to histology, as depicted in **Figure 2**. At multivariable analysis, histology was found to be a risk factor for LR (p=0.004) and DM (p=0.003), while grade was also a risk factor for DM (p=0.029). DDLPS were at higher risk for LR (p=0.010), while LMS had a higher risk of DM (p=0.03) (**Table 2**). DSS was independently predicted by tumor grade (p=0.020) and tumor histology, with SFT having a better DSS than DDLPS (p=0.009) and WDLPS having no sarcoma-related deaths.

Conclusion: Histology distribution of PSTS differs from the one consistently reported for RPS, with LMS being the most common subtype. The different histology distribution as well as the distinctive anatomic location were responsible for the

higher employment of multimodality therapies compared to RPS. Mirroring RPS, the pattern of recurrence and survival were similar, except for pelvic WDLPS having a very good DSS. Whether PSTS may be considered a distinct disease subset will need to be further studied and a standard approach to PSTS will have to be refined.

Table 1. Patients and tumour characteristics

	Overall operated patients		**WDLPS**		**DDLPS**		**LMS**		**SFT**		**Others**		
	n = 249	%	n = 29	%	n = 49	%	n = 64	%	n = 47	%	n = 60	%	p
Gender													**0.001**
Female	115	46.2	17	58.6	15	30.6	40	62.5	14	29.8	29	48.3	
Male	134	53.8	12	41.4	34	69.4	24	37.5	33	70.2	31	51.7	
Age *median (IQR)*	56	47-66	59	50-66	64	55-69	58	51-67	51	42-59	51	36-62	**<0.001**
ECOG													0.811
0	140	56.2	18	62.1	23	46.9	37	57.8	31	66.0	31	51.7	
1	77	30.9	9	31.0	18	36.7	19	29.7	12	25.5	19	31.7	
2	27	10.8	1	3.1	7	14.3	6	9.4	4	8.6	9	15.0	
3	3	1.2	0	-	1	2.0	1	1.6	0	-	1	1.7	
Missing	2	0.8	0	-	0	-	1	1.6	0	-	0	-	
Tumor size (mm) *median (IQR)*	130	80-198	195	160-220	170	106-223	100	62-157	120	70-165	120	80-177	**<0.001**
Laterality													**0.002**
Left	93	37.3	14	48.3	23	46.9	29	45.3	9	19.1	18	30.0	
Right	87	34.9	12	41.4	16	32.7	22	34.4	14	29.8	23	38.3	
Central	69	27.7	3	10.3	10	20.4	13	20.3	24	51.1	19	31.7	
FNCLCC Grade													**<0.001**
G1	69	27.7	29	100.0	4	8.2	11	17.2	22	46.8	6	10	
G2	99	39.8	0	-	38	77.6	28	43.8	14	29.8	17	28.3	
G3	67	26.9	0	-	7	14.3	24	37.5	1	2.1	35	58.3	
Missing	14	5.6	0	-	0	-	1	1.6	10	21.3	2	3.3	
Resected organs													**0.002**
0	27	10.8	7	24.1	4	8.2	2	3.1	8	17.0	6	10.0	
1	67	26.9	9	31.0	11	22.4	13	20.3	15	31.9	19	31.7	
2	70	28.1	9	31.0	12	24.5	22	34.4	13	27.7	14	23.3	
3	30	12.0	3	10.3	8	16.3	11	17.2	2	4.3	6	10.0	
≥4	55	22.0	1	3.4	14	28.6	16	25.0	9	19.1	15	25.0	
Median number (IQR)	2	1-3	1	0-2	2	1-4	2	2-4	2	1-2	2	1-4	

Table 2. Univariate and Multivariate analysis of competing risk for Local Recurrence, Distant Metastasis incidence, Overall Survival and Disease-free Survival.

	Local Recurrence						Distant Metastasis						Overall Survival						Disease-specific Survival					
	Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	**HR**	95% CI	p	**HR**	95% CI	p	**HR**	95% CI	p	**HR**	95% CI	p	**HR**	95% CI	p	**HR**	95% CI	p	HR	95% CI	p
Age	1.01	0.98-1.03	0.307	1.00	0.97-1.02	0.80	0.99	0.97-1.01	0.65	0.99	0.97-1.01	0.65	1.01	1.00-1.03	0.131				1.00	0.99-1.02	0.429			
Size	1.00	0.97-1.03	0.685	0.99	0.96-1.02	0.58	0.99	0.96-1.01	0.54	1.00	0.98-1.03	0.57	0.99	0.98-1.02	0.976				1.00	0.97-1.02	0.804			
FNCLCC Grade	1.30	0.91-1.87	0.140	1.00	0.53-1.88	0.99	2.09	1.52-2.87	**0.0001**	1.57	1.05-2.36	**0.02**	2.05	1.52-2.75	**<0.001**	1.48	0.57-1.80	**0.029**	2.32	1.69-3.20	**<0.001**	1.54	1.07-2.22	**0.020**
WDLPS	(ref)			(ref)			(ref)			(ref)			0.17	0.05-0.58	**0.04**	0.28	0.08-1.00	**0.05**						
DDLPS	5.62	1.74-18.1	**0.004**	5.46	1.50-19.8	**0.01**	3.78	0.86-16.5	0.07	2.43	0.52-11.3	0.25	(ref)			(ref)			(ref)			(ref)		
LMS	1.39	0.38-5.05	0.615	1.29	0.29-5.67	0.72	8.35	2.10-33.2	**0.03**	4.98	1.09-22.7	**0.03**	0.86	0.21-1.47	0.596	0.82	0.47-1.43	0.492	0.95	0.55-1.66	0.861	0.91	0.51-1.62	0.738
SFT	0.67	0.13-3.34	0.630	0.64	0.13-3.17	0.59	2.37	0.52-10.8	0.26	2.18	0.46-10.3	0.32	0.12	0.04-0.40	**0.001**	0.12	0.03-0.51	**0.004**	0.14	0.04-0.46	**0.001**	0.14	0.03-0.61	**0.009**
Other Histology	1.94	0.53-6.97	0.310	1.94	0.45-8.31	0.37	7.46	1.80-30.9	**0.006**	3.92	0.79-19.4	0.09	1.16	0.68-1.97	0.585	1.01	0.57-1.80	0.960	1.24	0.71-2.18	0.446	1.08	0.59-1.97	0.803

Figure 1

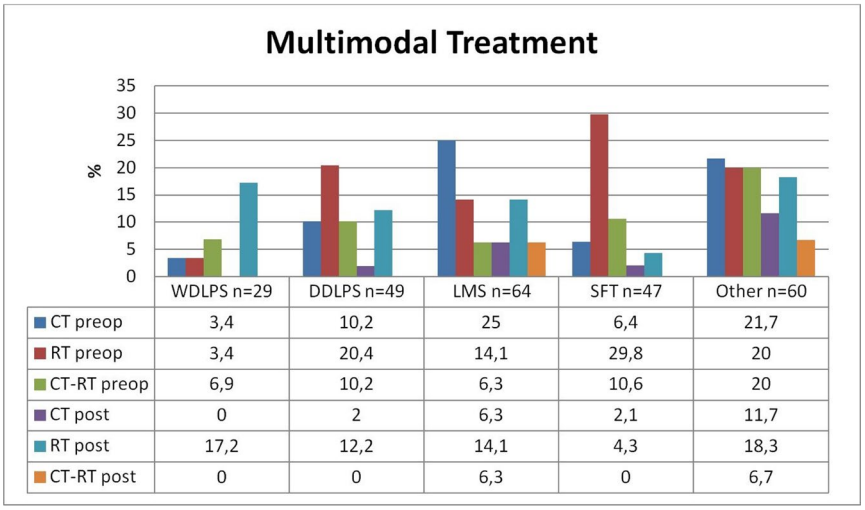
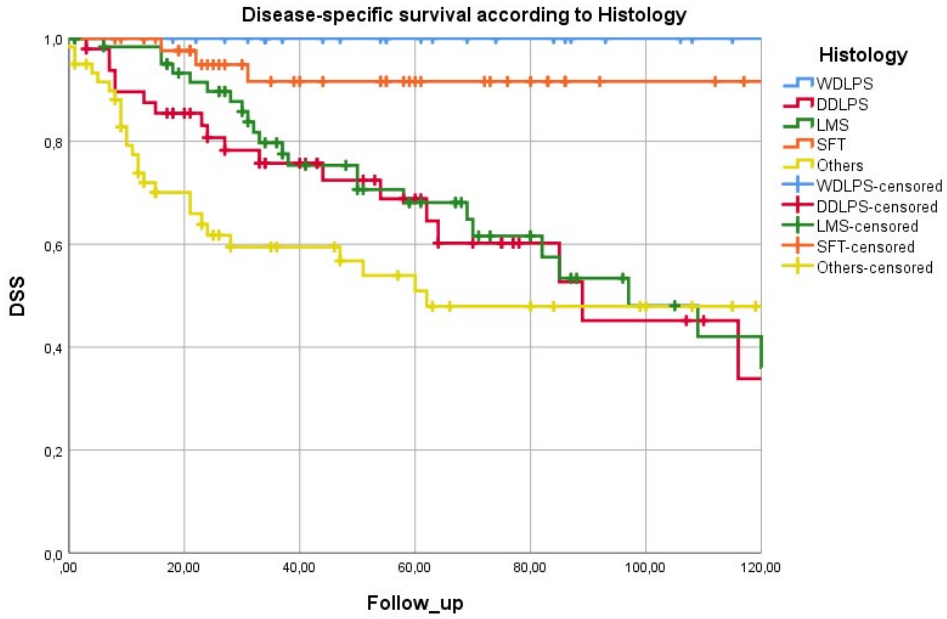


Figure 2



Poster #016 3437396

OSTEOSARCOMA ORGANOIDS DEMONSTRATE FUNCTIONAL AND THERAPEUTIC HETEROGENEITY DEPENDING UPON GEOGRAPHIC SITE OF ORIGIN WITHIN THE TUMOR

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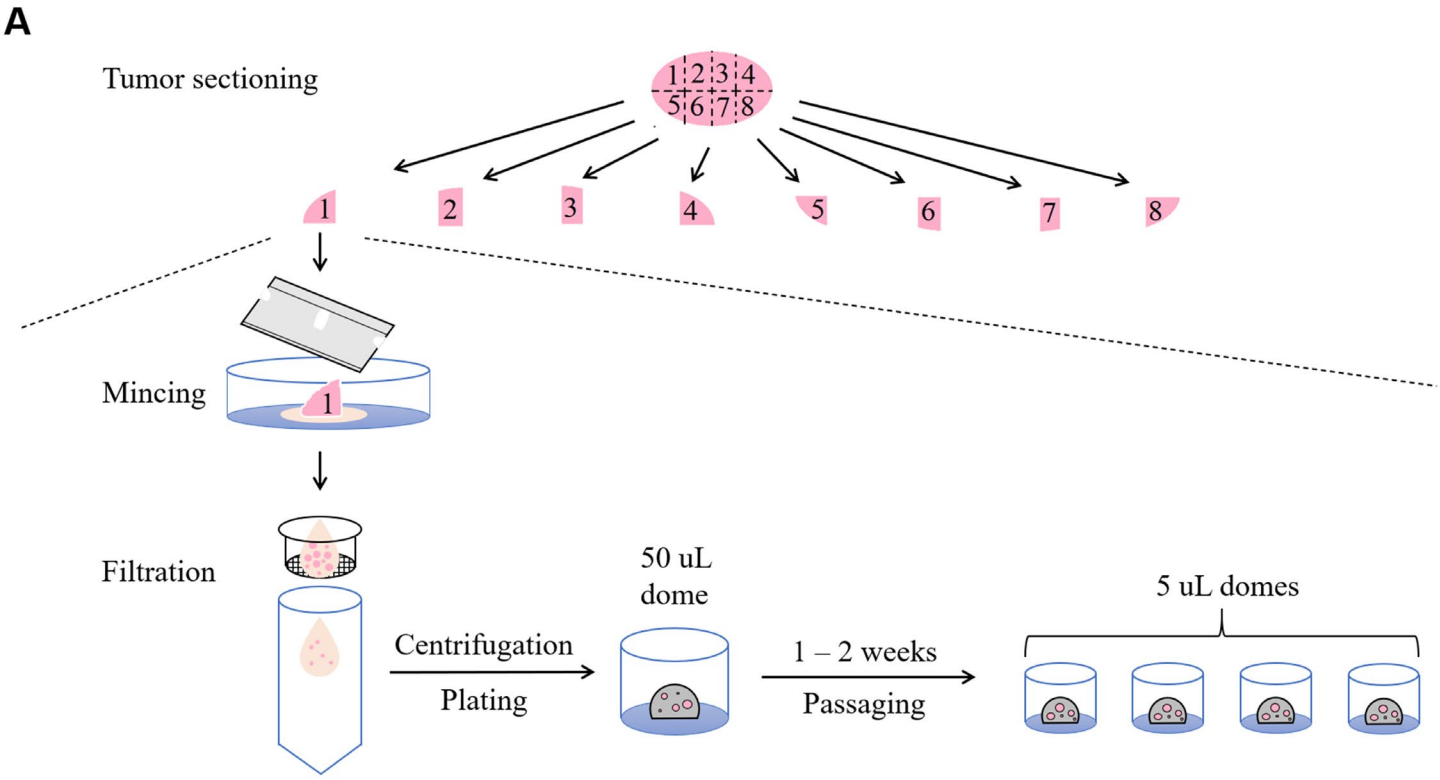
Objective: Osteosarcoma is the most common primary bone cancer in children and adolescents, and its prognosis has remained largely unchanged since the 1980s. The survival rate of patients with metastatic or recurrent disease remains especially poor, which is attributable to the development of resistance to standard chemotherapy. Osteosarcomas display marked intratumoral heterogeneity, which is thought to contribute to the development of chemoresistance. Presently, there is a lack of functional predictors that inform response to therapy, and there exist few ways to explore how the heterogeneity of osteosarcoma contributes to resistance. The aim of this study was to develop canine patient-derived 3D osteosarcoma organoids and use them to investigate the functional consequences of tumor heterogeneity on treatment response and resistance.

Methods: We developed organoids from spatially distinct pieces of two fresh canine osteosarcoma tumors and then treated these organoids with doxorubicin to estimate relative resistance and sensitivity. Histologically confirmed canine osteosarcoma samples were received fresh on-ice from veterinary partners. Tumor masses were sectioned into 10-15 pieces and their approximate locations within the tumor were documented. These spatially distinct tumor pieces were each processed and suspended in 70% Matrigel and 30% Dulbecco's modified Eagle's medium supplemented with 10% FBS to create organoids (Fig. 1). Organoids derived from each piece were treated with DMSO as a control and 500 nM doxorubicin for 72 hours. Organoid proliferation was tracked from time of organoid formation through the treatment period using IncuCyte confluence imaging software. Cell viability was measured after treatment using CellTiter-Glo® 3D Cell Viability Assay, and measurements were normalized to the DMSO control condition for each piece.

Results: Canine patient-derived 3D osteosarcoma organoids were successfully created from two fresh tumor samples. Organoids derived from different areas of one tumor sample demonstrated differential proliferative ability, ranging from 1.5- to 4.5-fold changes in confluence from plating to treatment time (Fig. 2A). Variation in sensitivity to doxorubicin was also observed, with cell viability in the treated organoids derived from distinct regions ranging from 16-80% in one tumor sample and 10-85% in the other (Figs. 2 and 3).

Conclusion: The successful development of patient-derived osteosarcoma organoids and demonstration of tumor functional heterogeneity provides a promising tool for enhancing our understanding of the mechanisms of osteosarcoma therapy resistance.

Figure 1. Organoids were created directly from fresh canine patient tumors. A) An optimized protocol for creating osteosarcoma organoids from spatially distinct regions of a tumor mass. B) Sectioning of tumor sample D089, with examples of organoids under light microscopy at 20x magnification.



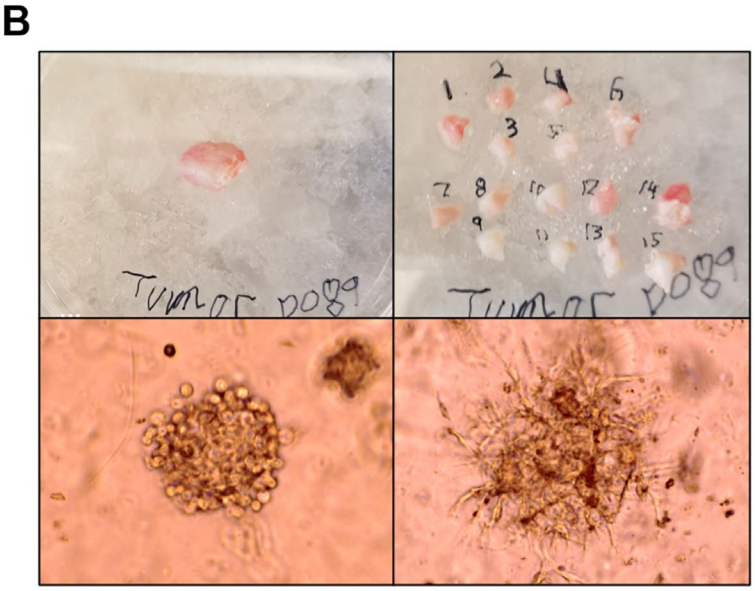


Figure 2. Patient-derived osteosarcoma organoids from tumor sample D089 exhibited functional heterogeneity.
A) Differences in organoid proliferation rate were observed across pieces. B) Differences in organoid proliferation in the presence of doxorubicin were found across pieces. C) Under (i) brightfield and (ii) phase imaging at 4x magnification, an organoid (red arrows) from D089 piece #4 is seen at plating (day 0), at treatment (day 2), and after treatment (day 5). D) Under (i) brightfield and (ii) phase imaging at 4x magnification, organoids (red and yellow arrows) from D089 piece #8 are seen at plating (day 0), at treatment (day 2), and after treatment (day 5). E) Heterogeneity in organoid sensitivity to doxorubicin was found across pieces. F) A spatial representation of the intact D089 tumor mass color-coded on a gradient demonstrating heterogeneity in doxorubicin response.

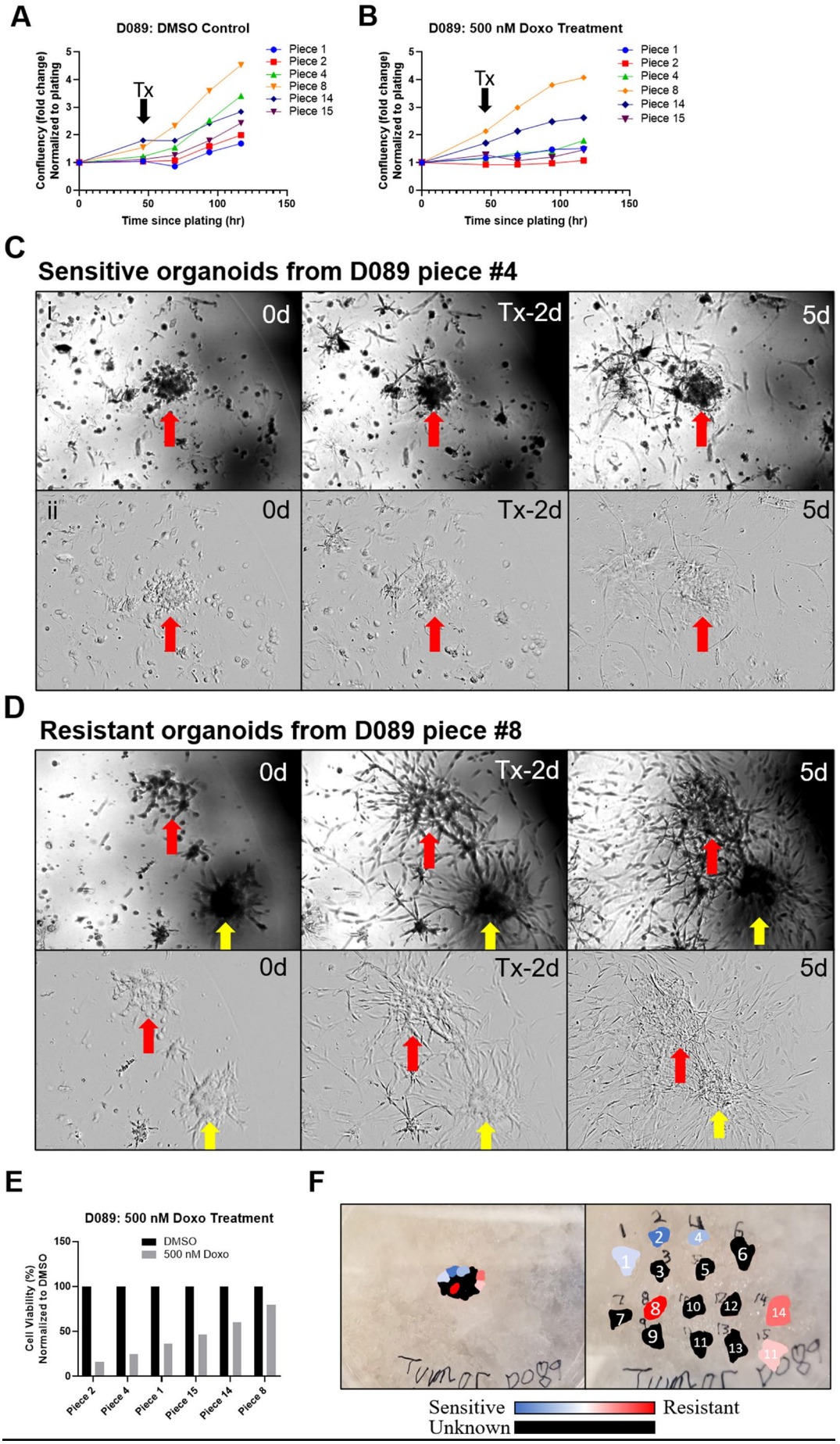
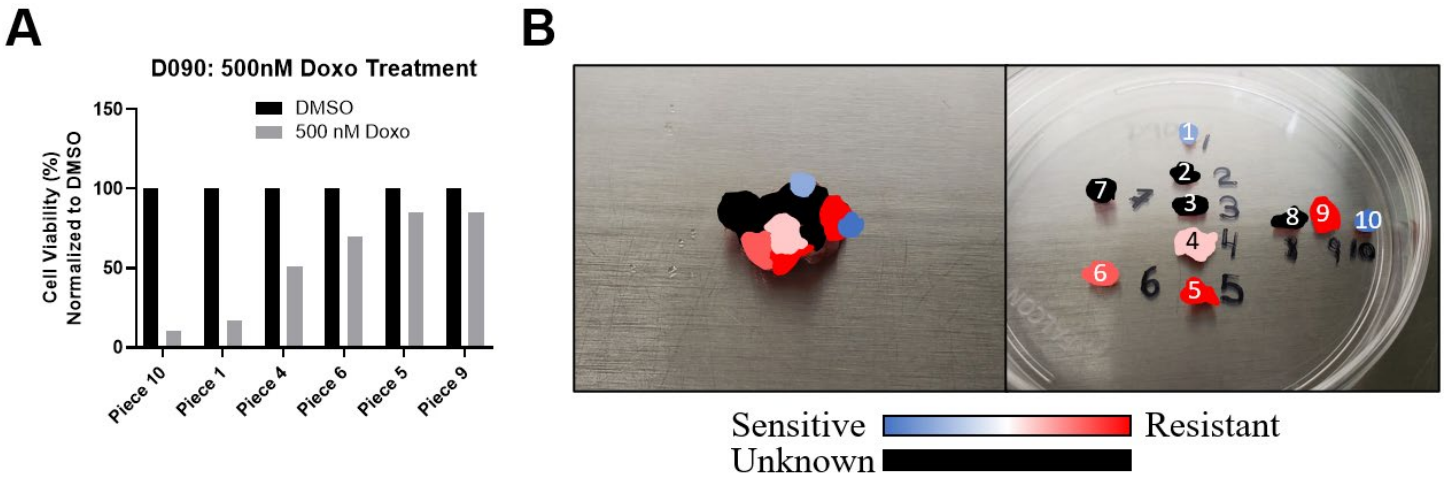


Figure 3. A heterogeneous response to doxorubicin was observed in patient-derived osteosarcoma organoids from tumor sample D090. A) Organoids from different pieces exhibited differential doxorubicin sensitivities. B) A spatial representation of the intact tumor mass color-coded on a gradient depicting the heterogeneity in doxorubicin response.



Poster #017 3437413

RADIOLOGICAL ANALYSIS OF TUMOR RESPONSE TO AN EFFECTIVE TYROSINE KINASE INHIBITOR (TKI), PEXIDARTINIB, IN TENOSYNOVIAL GIANT CELL TUMORS (TGCT) FROM THE PHASE 3 ENLIVEN STUDY

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Objective: ENLIVEN was a phase 3, placebo-controlled study of pexidartinib in patients with TGCT. Response rate was assessed by Response Evaluation Criteria in Solid Tumors v1.1 (RECIST, primary endpoint) based on sum of longest diameters (SLD) using magnetic resonance imaging (MRI). Measuring TGCT with RECIST is challenging due to the irregular shape and asymmetrical growth of the tumor. Also, RECIST does not assess local tissue damage, which is a primary clinical concern in TGCT. Therefore, ENLIVEN also included Tumor Volume Score (TVS, secondary endpoint) and modified-RECIST (sum of short-axis dimensions [SSD], exploratory endpoint) as additional MRI measures of tumor response. Both RECIST methods measure tumor size only linearly and in cm, whereas TVS measures tumor volume directly and in reference to the size of the specific joint or tendon involved (**Figure**). Thus, TVS relates tumor size more closely to local tissue damage and physical dysfunction. In ENLIVEN, TVS was defined as the estimated volume of the maximally distended synovial cavity or tendon sheath involved, measured in 10% increments. ENLIVEN also assessed joint damage directly using Tissue Damage Scoring (TDS). Here we compare local readings using only conventional RECIST with central readings that also included these additional MRI measures of disease progression and treatment response.

Methods: This retrospective analysis compared tumor responses on MRI determined by local experienced radiologists with responses determined by central expert radiologists at Spire Sciences. Responses were categorized as complete response [CR]: disappearance of all viable tumors; partial response [PR]: ≥30% decrease in SLD or SSD, or ≥50% decrease in TVS; stable disease [SD]: insufficient decrease to qualify as PR; or progressive disease [PD]: ≥20% and ≥5-mm increase in SLD or SSD from their smallest values during the study (nadir), or ≥30% increase in TVS from its nadir. TDS scored bone erosion, cartilage loss, and bone marrow edema/infiltration in multiple regions of each joint. Local readings used RECIST only, whereas central readings included RECIST, modified RECIST, TVS, and TDS (**Figure**).

Results: Serially acquired MRIs in part 1 of the study (up to week 25) from 60 evaluable patients randomized to pexidartinib treatment were assessed. Patients treated with placebo showed no tumor response by any of the MRI measures used (**Table**). However, response rates among patients treated with pexidartinib were high by locally assessed RECIST (36%), centrally assessed RECIST (39%), modified RECIST (56%), and TVS (56%). Kappa between local RECIST and central RECIST was 0.37, indicating that although response rates were similar (mild to moderate agreement) at the group level, discrepancies existed at the patient level. The most common disagreement between local RECIST and central RECIST was PR by local read being classified as SD by central read (**Table**). The most common discrepancy between local RECIST and central modified RECIST and TVS was SD by local read being classified as PR by central read.

No progression of baseline joint damage by TDS was seen during pexidartinib treatment. Response rates after continued pexidartinib treatment at January 2018 cutoff (10 months after initial data cut) and the May 2019 cutoff (26 months after initial data cut) were higher (**Table**). Differences between local and central readings were also observed after continued treatment (data not shown).

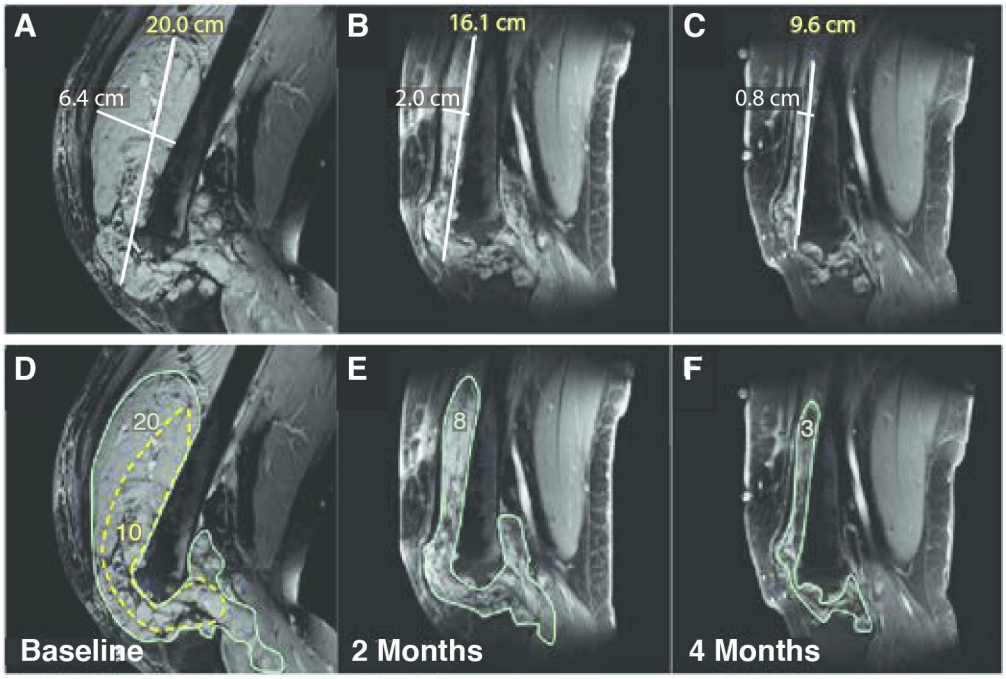
Conclusion: All of the MRI measures used in this study demonstrated significant response to treatment with pexidartinib. However, novel measures more specific to TGCT and performed centrally showed greater sensitivity to change than conventional RECIST. TDS further demonstrated no progression of joint damage in patients treated with pexidartinib. Combining novel measures of tumor size with assessments of joint damage may be beneficial for monitoring treatment of TGCT with TKIs in clinical practice.

Table. Comparison of overall tumor response by MRI local readings (RECIST) versus central readings (RECIST, modified RECIST, TVS) from the ENLIVEN study

		Local RECIST (SLD)*	Central RECIST (SLD)*	Central modified RECIST (SSD)*	Central TVS*
Overall tumor response rates					
Week 25 pexidartinib response rate, %[†]		36	39	56	56
Pexidartinib response rate at follow-up, %[‡]	Jan 2018 data cutoff (10 months after initial data cut)	NA	53	71	64
	May 2019 data cutoff (26 months after initial data cut)	NA	62	NA	66
Comparison of local vs central response determination in part 1 (up to week 25)[§]					
Patients with ≥1 difference, n (%)		—	27 (45)	33 (55)	32 (53)
Visits with ≥1 difference, n (%)		—	41 (36)	50 (43)	48 (42)
Type of difference across all visits, n (%) <u>Local vs central:</u> SD vs PR SD vs CR PR vs CR PR vs SD		—	 8 (7) 7 (6) 7 (6) 16 (14)	 27 (23) 8 (7) 6 (5) 6 (5)	 34 (30) 0 3 (3) 9 (8)
Kappa values[§]		—	0.37	0.33	0.27

*60 evaluable patients for local and central MRI readings; 1 patient did not have a valid baseline scan.
†March 2017 data cutoff (N = 61); responses per protocol were measured as CR or PR at either week 13 or 25.
‡January 2018 and May 2019 data cutoffs (N = 61 each); median treatment durations of 16 months and 17 months, respectively.
§Based on 115 MRI readings from March 2017 data cutoff. 55 of the 60 evaluable patients had 2 comparative readings (110 MRI readings), while 5 patients had only 1 comparative read (5 MRI readings) due to early discontinuation.
CR = complete response; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SLD = sum of longest diameters; SSD = sum of short-axis dimensions; TVS = tumor volume score.

Figure. Tumor response measured by RECIST, modified RECIST, and TVS following treatment with pexidartinib



RECIST (SLD) and modified RECIST (SSD)

TVS

Adapted from *N Engl J Med,* Tap et al, Structure-Guided Blockade of CSF1R Kinase in Tenosynovial Giant-Cell Tumor, 373, 428-437. Copyright © (2015) Massachusetts Medical Society. Reprinted with permission.

Mid-sagittal MRI shows a large tumor in the synovial cavity of the knee at baseline and after 2 and 4 months of treatment. The tumor is irregularly shaped and extends vertically in front of the femur, horizontally through the femorotibial joint space, and posteriorly down the leg.

The longest measurable linear dimension (RECIST) is 20.0 cm at Baseline (A). After 2 months of treatment (B) this measure decreased by 19% to 16.1 cm. By 4 months (C) it had decreased by 52% to 9.6 cm.

The short-axis dimension (modified RECIST), decreased much more: from 6.4 cm at Screening (A), to 2.0 cm (–69%) at 2 months (B) and 0.8 cm (–87%) at 4 months (C).

TVS, which scores tumor volume (solid outline) in increments of 10% of the estimated maximum volume of the involved synovial cavity (dashed outline), also showed greater responsiveness than RECIST, decreasing from a score of 20 at baseline to 8 at 2 months (E, –60%), and to 3 at 4 months (F, –85%).

TDS comprises multiple ordinal scales including for bone erosion, cartilage loss, subchondral marrow edema/infiltration, joint effusion, meniscal and ligamentous integrity and periarticular bursae and cysts. Extensive bone erosion and cartilage loss visible at baseline in this example did not progress during 4 months of treatment, and bone marrow edema resolved.

RECIST=Response Evaluation Criteria in Solid Tumors; SLD=sum of longest diameters; SSD=sum of short-axis dimensions; TVS=tumor volume score; TDS=tissue damage score.

Poster #018 3437421

A NOVEL PRE-OPERATIVE RISK SCORE TO GUIDE PATIENT SELECTION FOR RESECTION OF SOFT TISSUE SARCOMA LUNG METASTASES: AN ANALYSIS FROM THE UNITED STATES SARCOMA COLLABORATIVE

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Objective: Surgical resection is a widely accepted therapy for sarcoma lung metastases and has been associated with improved overall survival (OS). Our aims were to identify preoperative prognostic factors associated with OS and to develop a risk score to stratify patients being considered for lung metastasectomy.

Methods: Patients who underwent curative-intent resection of sarcoma lung metastases (2000-16) were identified from the US Sarcoma Collaborative. Patients with extrapulmonary metastatic disease or R2 resections of either primary tumor or lung metastases were excluded. Primary endpoint was OS.

Results: Three hundred and fifty-twopatients met inclusion criteria. Mean age was 53yrs and 57% were male. Location of primary tumor was truncal/extremity in 85% (n=270) and retroperitoneal in 15% (n=49). The most common histiotypes were undifferentiated pleomorphic sarcoma (26%), leiomyosarcoma (18%), and synovial sarcoma (15%). Forty-nine percent (n=171) of patients had solitary and 51% (n=180) had multiple lung metastasis. Medan number of lung nodules was 2. Median OS was 49 months with a 5-year OS of 42%.

On multivariable analysis, age ≥55 (HR 1.77), retroperitoneal tumor location (HR 1.67), R1 primary tumor resection (HR 1.72), and multiple (≥2) lung metastasis (HR 1.77) were independently associated with decreased OS (all $p<0.05$). Assigning one point for each factor, we developed a risk score from 0-4. Patients with 0 and 1 risk factor had similar 5-year OS (61 vs 48% $p=0.335$) and patients with 2, 3, and 4 risk factors had similar 5-year OS (17 vs 10 vs 0%, $p=0.245$ and $p=0.645$, respectively). Thus, patients were divided into two risk groups: low (0-1 factor) and high (2-4 factors). When stratifying patients by risk group, the low-risk group (n=159) had significantly better 5-year OS compared to patients in the high-risk group (n=108) (51 vs 16%, $p<0.001$) (Fig. 1).

Conclusion: Using our multi-institutional cohort, we identified four characteristics that in aggregate portend a worse OS and created a novel prognostic risk score for patients with sarcoma lung metastases. Given that patients in the high-risk group have a projected OS of <20% at 5 years, this risk score is an important tool to aid in preoperative counseling, patient selection for pulmonary metastasectomy, and consideration for multimodal therapy.

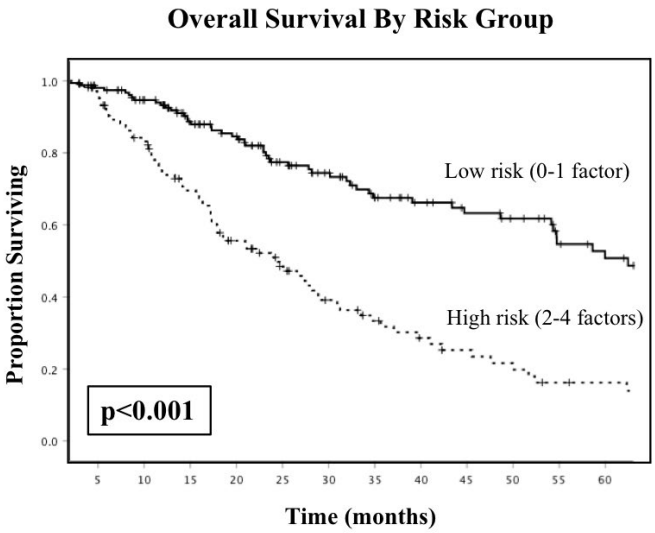

Figure 1. Stratification and survival for patients who underwent lung metastasectomy by risk factor group (risk factors included: age ≥ 55, retroperitoneal primary tumor, R1 primary tumor resection, and multiple lung metastasis)

Poster #019 3437427

THE ACCURACY OF A NOVEL SONOGRAPHIC SCANNING AND REPORTING PROTOCOL TO SURVEY FOR SOFT TISSUE SARCOMA LOCAL RECURRENCE: RESULTS OF A PROSPECTIVE PILOT STUDY

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Objective: Following resection of truncal and extremity soft tissue sarcomas (STS), magnestic resonce imaging (MRI) is the imaging modality primarily used to survey for local recurrence. However, this imaging modality is costly, time-consuming, necessitates repeated gadolinium exposure, and can be limited by patient movement or the presence of metal. Two-dimensional ultrasonography (US) is a potential alternative surveillance modality. The aim of our pilot study was to determine the accuracy of a novel US scanning and reporting protocol to detect local recurrences and to compare US and MRI accuracy and agreement.

Methods: In this IRB approved prospective study, consecutive patients presenting for MRI surveillance after resection were enrolled and underwent same day US. Blinded to clinical information, the US scanner characterized lesions using a novel lexicon and risk scoring system. Variables within the lexicon were: mass shape, mass chronicity, mass size, posterior acoustic behavior, echotexture, vascularity, shear wave elastography, and volume. Primary outcome was local recurrence defined either by histology or a subsequent MRI scan confirming the presence or absence of recurrence. A Fisher's exact test and Kappa test was performed to assess of the significance and agreement between US, MRI and outcome. A t-test was used to compare lesional volume and shear wave elastographic (SWE) properties between recurrent tumor and benign tissue.

Results: A total of 68 US scans were performed on 55 patients. Among the 68 enrolled patients, outcome data was available for 54 US scans (79%) derived from 45 unique patients--the study cohort hence forth refers to the 55 US scans with available outcome data. The local STS recurrence rate in the study cohort was 26.6%. The most common recurrent histologic subtypes were liposarcoma, synovial sarcoma and UPS.

A total of 16 lesions were identified on imaging of which 11 were seen on US and 15 on MRI. Among the nine patients where US detected a mass that was proven recurrence, the mean total risk score was 9.8 (range 7-13). All recurrent, high-grade sarcomas had a score of at least 8. There were three nodules detected by US that were benign with a mean total risk score of 4.3. The overall accuracy (92%) of diagnosing a recurrence was similar between US and MRI confirming the validity of the US lexicon. However, US was less sensitive (75.0% vs. 91.7%) but more specific (97.6% Vs. 92.9%) than MRI in detecting local recurrences. There was strong agreement between US and MRI with regard to the primary outcome (k = 0.787 and 0.801, respectively).

Conclusion: In this cohort, US had the same accuracy in the detection of STS local recurrences compared to MRI. Using this lexicon a total score of > 4 is concerning for recurrent tumor and should warrant at least a contrast enhanced MRI if not a biopsy. A future multi-center prospective trial using the lexicon and scoring system should be performed to validate these findings and acquire more data. This could lead to incorporation of US in surveillance algorithms of patients with truncal and extremity STS with an associated decreased cost to the healthcare system.

Poster #020 3437455

HISTOLOGICAL VARIATION AFTER PRE-OPERATIVE HYPOFRACTIONATED VERSUS STANDARD FRACTION RADIOTHERAPY IN SOFT TISSUE SARCOMAS

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Objective: Neoadjuvant standard fractionated radiation therapy (SFRT) is typically administered for soft tissue sarcomas (STS) followed by resection 4-6 weeks later. Hypo-fractionated radiation therapy (HFRT) is an appealing alternative, administering higher doses of radiation per fraction in a shorter interval. This study aims to review histological changes of resected STS treated with SFRT versus HFRT.

Methods: An IRB approved review was undertaken of prospectively banked tissue samples of 10 individual STS (9 patients), which had been biopsied and resected at our institution from 2000 to 2019. All patients were treated with neoadjuvant radiation therapy (RT). SFRT was defined as doses of 45- 50.4 Gy in 25-28 fractions. HFRT courses ranged from 20-30 Gy in 5 fractions. Characteristics reviewed included: tumor infiltrating lymphocytes, necrosis, residual viable cells, hyalinization/ fibrosis, and tumor infarction. The pathologist was blinded to the identity and outcomes of the patients. Patient characteristics, treatment course/technique, and outcomes were independently collected on chart review by a provider blinded to the histologic analysis. The histologic data was then linked to the patient data and analyzed comparing outcomes based upon type of RT.

Results: Median age of patients was 64 years (range 38- 85). Six sarcomas were retroperitoneal, while other sites included: 2 lower extremities, 1 buttock, and 1 scapula. The most common histology was myxofibrosarcoma (30%). Other subtypes were liposarcoma, spindle cell, leiomyosarcoma, and undifferentiated pleomorphic sarcoma. Three sarcomas were treated with HFRT (30%) and 7 with SFRT (70%). Chemotherapy was administered prior to RT in 3 cases. All sarcomas had surgical resection after RT. Recurrences occurred in 1 HFRT case and 2 SFRT cases. Table 1 includes distribution of cases according to histological characteristics.

Conclusion: The correlation of the two courses of neoadjuvant RT with post-therapeutic histology demonstrates valuable information on tumor response. Although our review depicted limited necrosis in both cohorts, with neither achieving >90%, the HFRT cohort had a comparable percentage of viable tumor to the SFRT cohort. HFRT did have a higher mean percentage of hyalinization/fibrosis, which has been shown in a previous study to be associated with favorable outcomes. No immunotherapeutic markers are known to correlate with sarcoma response. Further research is needed to clarify differences in immuno-infiltrating cells in our cohorts. Study limitations include the small size and limited follow-up; further research is needed to clarify the potential equivalence of hypo-fractionated RT relative to standard RT when studying the pathologic tumor response of soft tissue sarcomas.

Table 1

	SFRT	HFRT
Viable Tumor Mean (SD)	58.6% (0-100%)	56.7% (2-88%)
Necrosis Mean (SD)	13.6% (0-40%)	1% (0-3.0%)
Hyalinization/ fibrosis Mean (SD)	27% (0-98%)	41.7% (7.0-98%)
Infarction Mean	5.2% (0-20.0%)	.7% (0-2.0%)
Immuno- infiltrating Cells		
Absent	71.4%	100%
Present	28.6%	0%

Poster #0221 3437674

STRIVE-01: PHASE I STUDY OF EGFR806 CAR T CELL IMMUNOTHERAPY FOR RECURRENT/REFRACTORY SOLID TUMORS IN CHILDREN AND YOUNG ADULTS

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Objective: The epidermal growth factor receptor (EGFR) is a cell surface tyrosine kinase receptor expressed in a diverse group of tissues and associated with cell proliferation and differentiation. Expression of wild-type EGFR and activating mutations are described in neoplastic conditions, and are associated with aggressive disease, chemotherapy resistance, and increased metastatic potential. Published data and EGFR immunohistochemistry (IHC) performed on tissue microarrays indicate that 15-40% of pediatric solid tumors express EGFR.

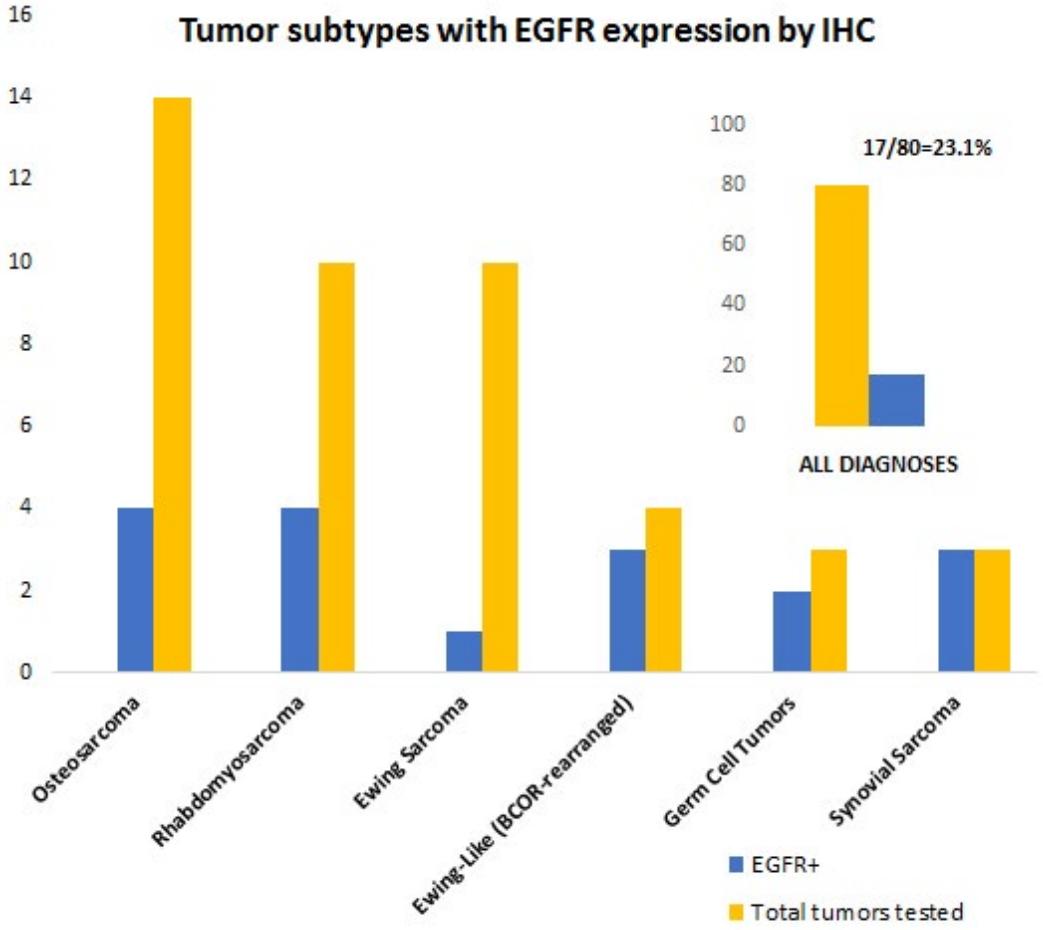
Chimeric Antigen Receptor (CAR) T cell immunotherapy is an emerging therapeutic modality that requires discrimination between tumor recognition and normal tissues. The unique EGFR monoclonal antibody (mAb) 806 selectively binds to an epitope that is conformationally hidden when EGFR is tethered but revealed when tethering is perturbed as is the case when EGFR is overexpressed, truncated, or by a variety of ECD missense amino acid substitutions. Thus, it is an attractive candidate for use in the development of an EGFR-specific CAR for employment in adoptive T-cell therapy for EGFR-expressing relapsed or refractory pediatric solid tumors. In addition, T-cells can be co-transduced to express two different CARs and these cells become bispecific for two antigens. We hypothesize that engrafting bispecific EGFR806 with CD19 dual CAR T-cells will permit the expansion and retention of function of large numbers of CAR T-cells outside the solid tumor that can then infiltrate solid tumors in large numbers.

Methods: We designed a Phase I study to enroll pediatric and young adult patients with EGFR-expressing recurrent/refractory solid tumors to examine the safety and feasibility of administering autologous, peripheral blood-derived T cells that have been genetically modified to express a second generation EGFR806-specific CAR alone (Arm A) or in combination with a CD19-specific "driver" CAR (Arm B). The primary objectives of the study are to assess the feasibility of deriving the cell products and the safety of the T-cell product infusion, to determine the maximum tolerated dose (MTD) using a 3+3 design, to define the dose limiting toxicities (DLTs), and to describe the full toxicity profiles of each arm. Arm B will proceed after establishment of the MTD for Arm A. The secondary objectives are to study the *in vivo* engraftment and persistence of transferred cells in the peripheral blood and tumor tissues or normal tissues as well as the capacity of the co-expressed CD19 CAR to augment T-cell engraftment and prolong persistence as determined by the duration of B-cell aplasia.

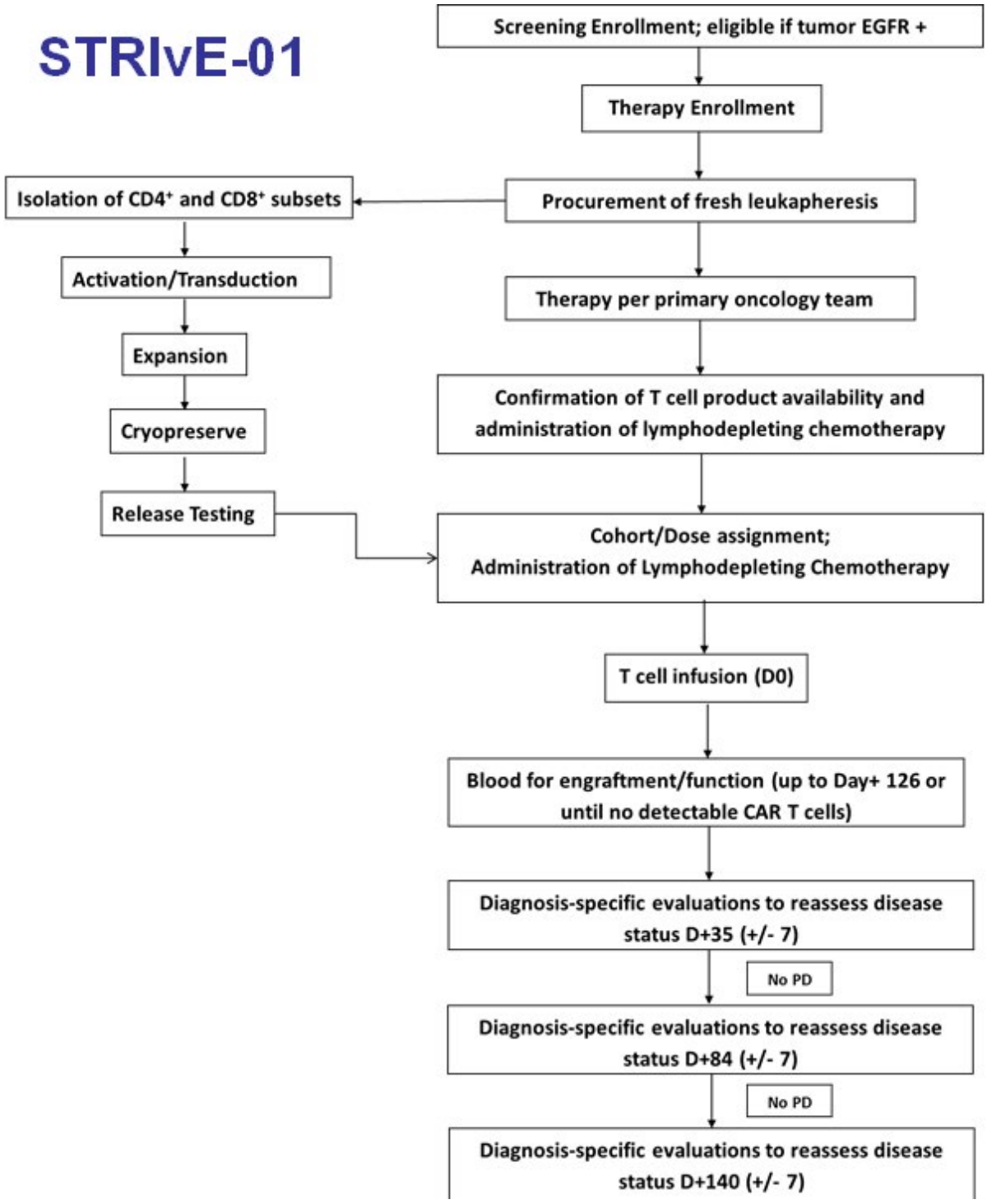
Results: The trial opened in August of 2018. As of June 25, 2020, 5 subjects have enrolled and 4 subjects (3 evaluable) have been treated on Arm A, dose level 1 without DLT, nor evidence of off-tumor, on-target effect. In an analysis of 80 tumors tested for eligibility, we observed EGFR expression by IHC in 17/80 (21.3%) tumors, including BCOR fusion sarcoma (3/4), germ cell tumor (2/3), osteosarcoma (4/14), synovial sarcoma (3/3), rhabdomyosarcoma (4/10), and Ewing sarcoma (1/10).

Conclusion: T cell products have been successfully manufactured for the first 5 enrolled subjects. No DLT or safety events were observed for the three evaluable subjects treated on Arm A, dose level 1. We are now enrolling on Arm A, dose level 2. It is still too early to make any conclusions about the trial.

EGFR evaluation by IHC for eligibility on STRIvE-01 demonstrates an expected rate of EGFR positivity in a variety of histologies: EGFR IHC results for histologies with at least one positive result and for all tumors tested.



Experimental Schema: Subjects undergo apheresis to obtain T cells from which the CAR T cell products are manufactured. During the manufacturing period, subjects may return to the care of their primary physician and may receive additional cancer-directed therapy. When the subject's CAR T cell product meets manufacturing release criteria, the CAR T cell infusion is scheduled. Lymphodepleting chemotherapy is completed at least 48 hours prior to CAR T cell infusion. Subjects are monitored for persistence of peripheral blood CAR T cells and undergo disease specific evaluations at regular intervals.



Poster #022 3437802

NICLOSAMIDE STEARATE PRODRUG THERAPEUTIC (NSPT) ENHANCES MITOCHONDRIAL PROTON LEAK AND INDUCES POTENT CYTOTOXICITY IN OSTEOSARCOMAS

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Objective: Osteosarcoma (OS) is the most common primary bone tumor in children. For many of these children, a combination of surgery and highly toxic chemotherapy prolongs their survival. However, many of these survivors suffer from shortened life spans due to chemotherapy-related complications, such as cardiotoxicity. Further, for patients who present with metastatic disease the 5-year overall survival is just 30%. There is a pressing need to identify safer, non-toxic, and effective chemotherapeutic alternatives to treat osteosarcoma. A novel chemotherapeutic, Niclosamide Stearate Prodrug Therapeutic (NSPT), has recently been developed and evaluated. NSPT's mechanism of action, low toxicity profile, and efficacy in treating micrometastatic OS have been previously described. It is hypothesized that NSPT acts via alteration of mitochondrial function by uncoupling the electron transport chain across the inner mitochondrial membrane. In this study we evaluated the bioenergetic effect of NSPT in OS mitochondria and its ability to induce apoptosis.

Methods: Niclosamide, a poorly bioavailable drug when taken orally, was formulated as Niclosamide Stearate Prodrug Therapeutic (NSPT) using a rapid solvent-solvent exchange method originally developed by the Needham Lab. Their size was measured utilizing Dynamic Light Scattering. Metabolic differences in NSPT-treated canine and human osteosarcoma cells (143B, MG-63, D418, and D17) were quantified using seahorse assays after three hours and three days of treatment. For the three-hour condition, the cells were treated with their respective half maximal inhibitory concentration (IC50) and half of their IC50. For the three-day condition a much smaller dose (1/6 of the cell's IC50) was utilized. Cytotoxicity of NSPT was measured in monoculture and spheroid cultures using IncuCyte® S3 imaging, which allowed for a quantitative measure of growth inhibition (% confluence) and apoptosis (caspase 3/7 activity and the quantified fluorescent read out). Cell viability was quantified at endpoint using CellTiter-Glo® Luminescent Cell Viability Assay.

Results: NSPTs were measured to have an average particle size of 25.39 +/- 10.23 nm and polydispersity index < 0.3. As shown in Figure 1B, NSPTs induced a significant increase in proton leak in both the canine cell lines (D17, $p = 0.01$; D418, $p = 0.001$) and human cell lines (MG-63, $p = 0.04$; 143B, $p = 0.01$). In Figure 1C, there was also a significant increase in aerobic glycolysis (ECAR; D17, $p = 0.0003$; D418, $p < 0.0001$; MG-63, $p < 0.0001$). These findings, especially increased proton leak, were maintained for up to three days in human OS cell lines. These alterations in metabolic capacity induced subsequent apoptosis and cytotoxicity of both monoculture and 3D spheroid cultures (Figure 2A, B, C).

Conclusion: Osteosarcomas rely on aerobic glycolysis to fulfill a large proportion of their metabolic needs as it produces a favorable environment for growth and may increase its metastatic potential. Although this may be advantageous for their survival, it may also leave osteosarcomas energetically vulnerable, as any disruption in the structures they use to maintain their basal function could leave them with very little reserve to prevent cell death. For this reason, a drug that disrupts the mitochondria could be an effective treatment for osteosarcoma, as it would alter the bioenergetics of the cell and the increased proton efflux would promote an environment favorable for apoptosis. Our results show that NSPT increases proton leak in mitochondria of osteosarcoma cells and that this may be one of the ways in which NSPT is able to induce apoptosis. Further, this effect is conserved in both human and canine osteosarcomas, which may indicate it will have a robust effect against a multitude of osteosarcoma phenotypes. These findings provide further mechanistic support for the use of NSPT as a promising chemotherapeutic for micrometastatic or established metastatic disease in osteosarcoma patients.

Figure 1: A) Diagram of the proposed mechanism of action of NSPT and, thus, niclosamide on the inner mitochondrial membrane. It is thought that niclosamide acts as a shuttle, carrying protons from the matrix to the intermembrane space. B) Mitochondrial stress test after 3 hours of treatment showing that all cell lines tested demonstrate a significant increase in proton leak. This supports the uncoupling process diagrammed in panel A. C) ECAR, a measure of aerobic glycolysis, for each of the cell lines. The canine cell lines appeared to have an increase in aerobic glycolysis. This pattern was not observed in the human cell lines.

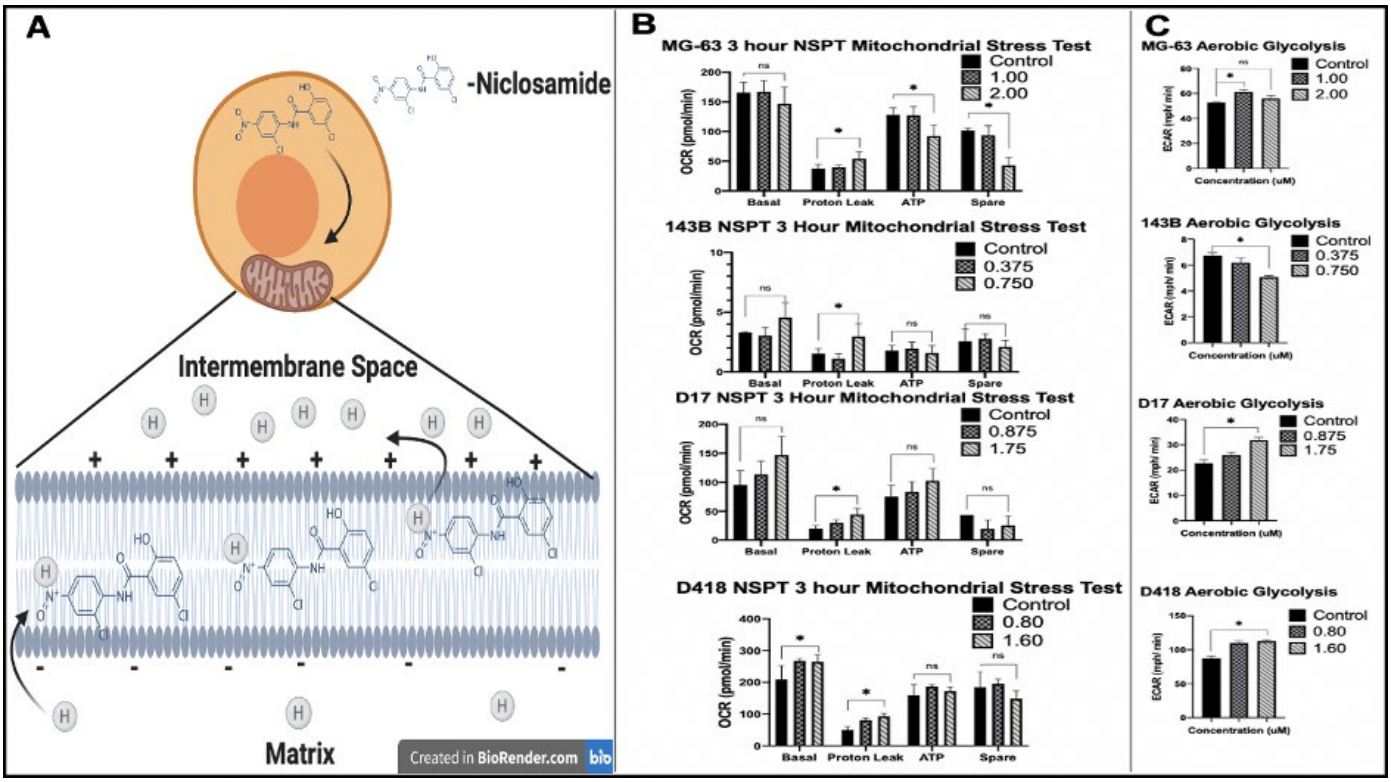
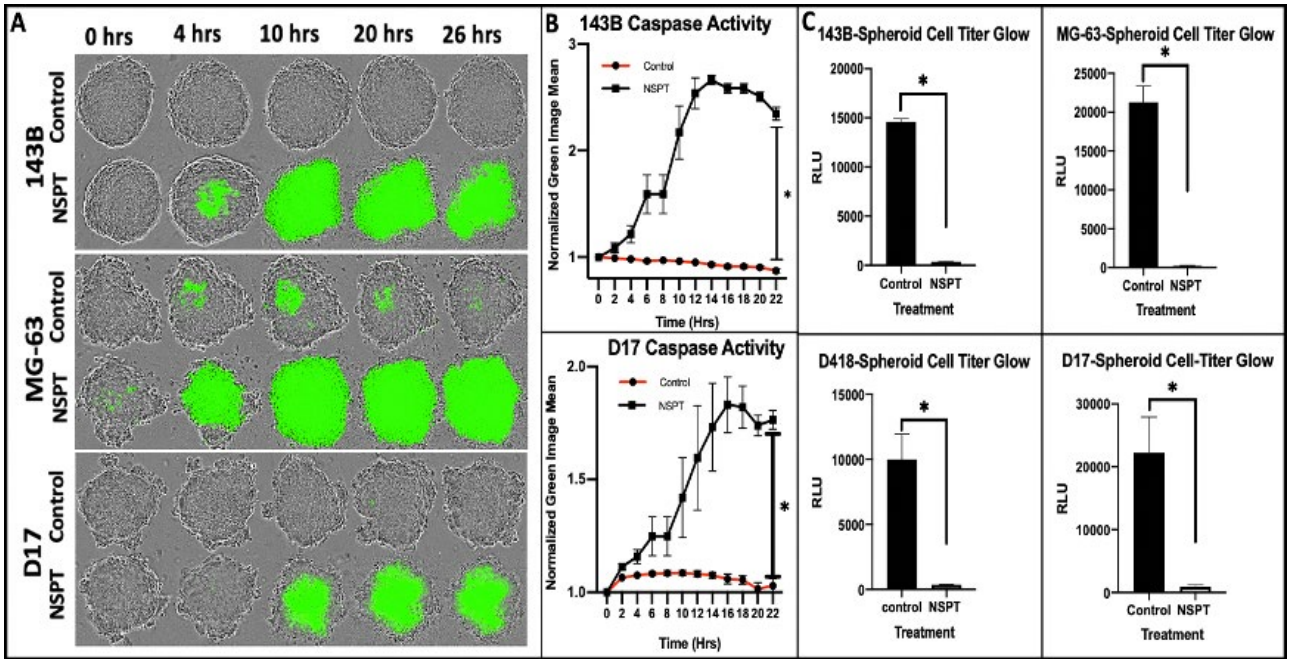


Figure 2: A) Osteosarcoma cell lines treated with either control or NSPT and a caspase 3/7 fluorescent marker. In all cell lines, the level of caspase 3/7 activity was markedly increased in the treatment group compared to the control. B) Significant differences were observed in the green image mean, indicating level of apoptosis, in the cell lines over a 24-hour period. C) Cell-titer glow end point assays showing that the number of viable cells in the treatment group was lower than that of the control group.



Poster #023 3438818

MAGNETIC RESONANCE GUIDED HIGH INTENSITY FOCUSED ULTRASOUND IN COMBINATION WITH THERMOSENSITIVE LIPOSOMAL DOXORUBICIN AS A NOVEL TREATMENT FOR RHABDOMYOSARCOMA

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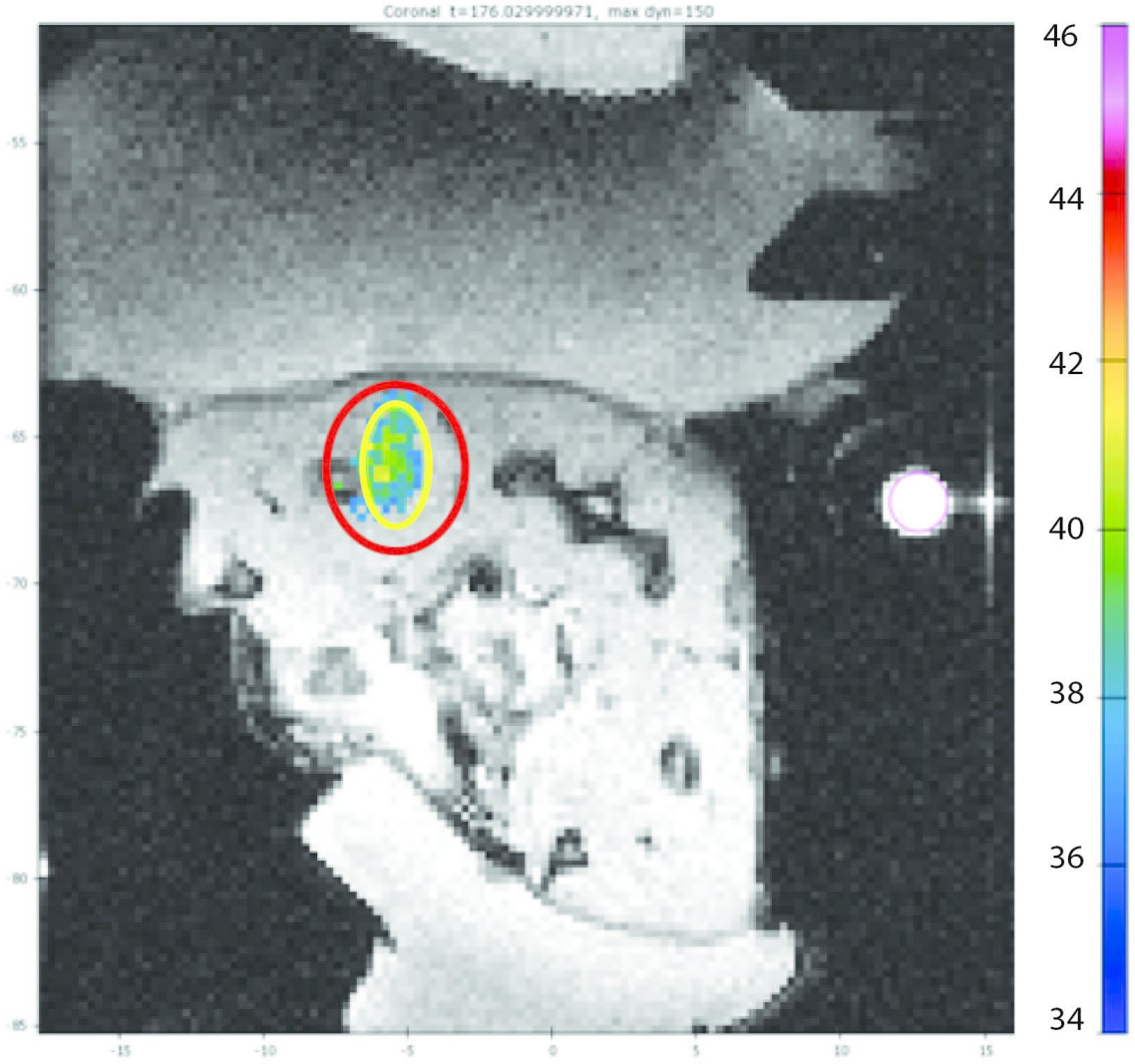
Objective: Rhabdomyosarcoma (RMS) is a tumor of skeletal muscle that predominantly affects children and young adults. The most common RMS subtypes are embryonal (ERMS) and alveolar (ARMS). Current treatment includes vincristine-based chemotherapy, radiation and/or surgery. Overall five-year survival is ~30% in the most aggressive form of the disease, which has remained stagnant in the last two decades. In relapsed RMS, alternate chemotherapy includes doxorubicin. However, there is significant cardiotoxicity with doxorubicin use. Thus, new treatments need to be developed to increase efficacy while reducing toxicity. An alternate form of doxorubicin is encapsulated in a thermosensitive liposome (TLD) and has been used in the treatment of breast and liver malignancies. Liposomal encapsulation has the potential to reduce systemic exposure. Doxorubicin is rapidly released from the thermosensitive liposome when it reaches a temperature of 41°C. To heat the drug, our group is using magnetic resonance guided high intensity focused ultrasound (MRgHIFU), which combines real time imaging to generate a non-invasive, non-ionising, localised, and controlled hyperthermia (HT) (Figure 1). HT has its own cytotoxic effects as well as altering the immune response to the tumor. We propose that the use of MRgHIFU to stimulate release of TLD in vivo in a murine ERMS model will localize doxorubicin in the tumor while limiting systemic toxicity and may augment immunoresponsiveness.

Methods: Our laboratory previously generated an RMS syngeneic mouse model by overexpressing mutant FGFR-4V550E, a mutation also found in human RMS, in immunocompetent p53 heterozygous mice. 2-3 weeks after injecting the tumor derived cells, we screened the mice using a 7T MRI to determine both the location and size of the tumor. The mice were then divided into either HT or non HT groups and were treated for 10 or 20 minutes with either TLD or standard doxorubicin. HT was delivered with a small animal MRgHIFU unit (IGT, Bordeaux, France) compatible with 7T MRI and controlled by a software for MRI-guided procedures made by our team. These time durations were chosen based on the feasibility to maintain the mouse's core body temperature, while heating the tumor. We completed high-performance liquid chromatography (HPLC) to analyze the percent of the initial drug dose found in the tumors and plasma. HPLC was compared between TLD and standard doxorubicin after either 10 or 20 minutes of HT to evaluate the role that heating duration played in drug release. Immunohistochemistry was used to assess immune cell infiltrate both before and after treatment.

Results: We were able to consistently maintain the temperature in the tumor at the drug release point with an average temperature of 40.6±1.3°C. There was a significantly higher amount of drug within the tumor after 20 minutes of heating with TLD compared to an unheated control with TLD. In addition, there was a significantly higher amount of TLD remaining in the plasma after 20 minutes with no heating compared to standard doxorubicin in both heated and unheated tumors. All tumors had immune infiltrate and further analysis of specific cell types is ongoing. We are also evaluating the impact of this treatment on survival and if doxorubicin accumulates in heart, liver, and kidneys to determine systemic release and toxicity.

Conclusion: We have developed an immunocompetent murine model of RMS that is able to be targeted with MRgHIFU. We propose that this treatment combination of MRgHIFU generated HT with TLD will allow for a more targeted drug delivery to the tumor leading to improved response, while minimizing serious systemic toxicities and with the potential to alter the immune response. This would significantly reduce the morbidity of treatment for this susceptible patient population. Therefore, the proposed preclinical project would form the basis for the translation of the use of MRgHIFU with TLD into the pediatric oncology clinic.

Figure 1 Axial MR section of a mouse hindlimb during MRgHIFU treatment where the tumor is circled in red and the treating area is circled in yellow, corresponding temperatures are seen on the right hand side. The target temperature was 42°C



Poster #024 3439734

SOFT TISSUE SARCOMA: IS THERE A SURVIVAL GAP BETWEEN MIDDLE-AGED AND ELDERLY PATIENTS?

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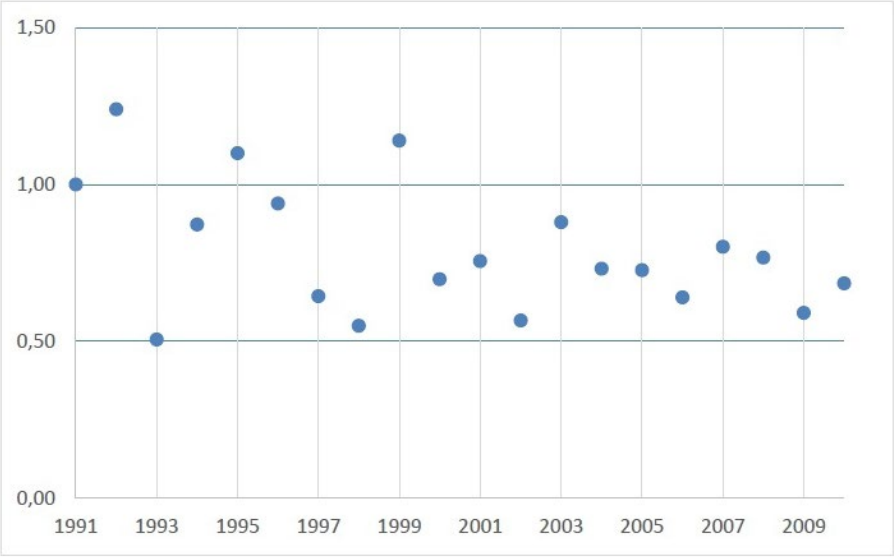
Objective: Recent research showed that a third of Soft Tissue Sarcoma (STS) cases occur in elderly patients aged 65 and older. However, research in other types of cancer shows a widening survival gap between middle-aged, aged and older patients. A better understanding of the incidence and treatment differences between age groups is mandatory in order to preserve the most optimal treatment and thereby close the gap between different age groups. In this study, our aim was to analyze the epidemiologic, clinical and treatment data among the elderly STS population compared with younger adult patients. Furthermore, we sought to compare survival rates over time between middle-aged (<65 years), aged (65-74 years) and elderly (>75 years) STS patients.

Methods: All 15 294 with Soft Tissue Sarcoma diagnosed between 1990 and 2016 were selected from the Netherlands Cancer Registry. Relative survival was calculated. Relative Excess risks of death (RER) were estimated using a multivariable generalized linear model with a Poisson distribution.

Results: There were significant changes in the treatment over time. Patients more often received radiotherapy (from 26% to 35%), while less older patients were operated on. Overall, there was a significant increase in the 5-year relative survival from 51.3% in 1991-1995 to 53.3% in 2011-2014 (p = 0.11). Relative 5-year survival increased significantly for middle-aged patients (RER 0.99 (95% CI = 0.97-0.99, p=0.001)) after adjustment for sex, age, stage and treatment, but did not change significantly for elderly (RER 0.99 (95% CI = 0.97-1.00, p 0.12)) and aged patients (RER 0.99 (95% CI = 0.97-1.00, p=0.150)).

Conclusion: The last decades, no major changes were made in the treatment of patients with soft tissue sarcoma. This study showed a significant increase in relative survival for patients with STS. The gap in relative survival between younger patients (<65 years) and older patients (>75 years) grows however. A more tailor-made treatment plan for older patients may hopefully lead to a closure of this gap.

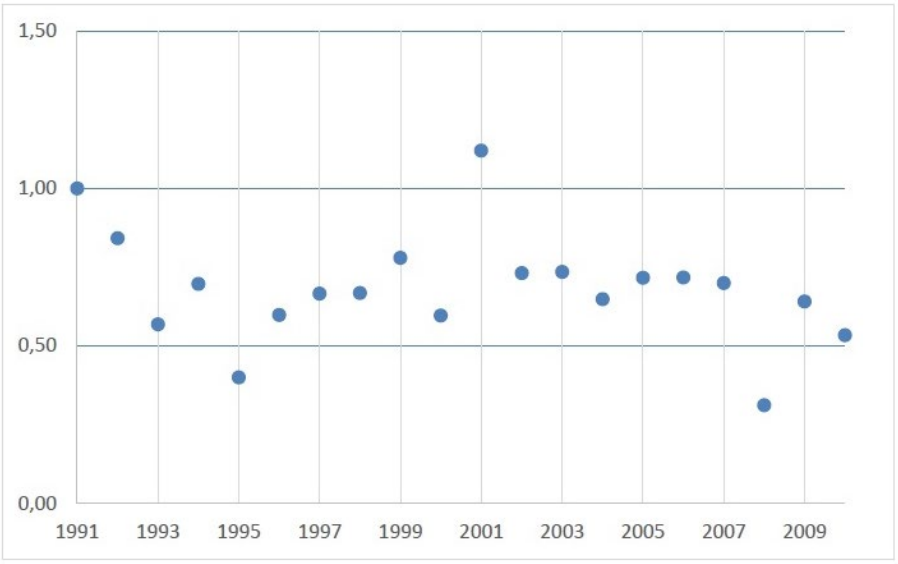
RER in middle aged patients



RR Continue: 0.985 (0.972-0.998) p=0.025

FIGURE 1A: RER in middle-aged patients (<65 years) adjusted for age, sex, grade and treatment

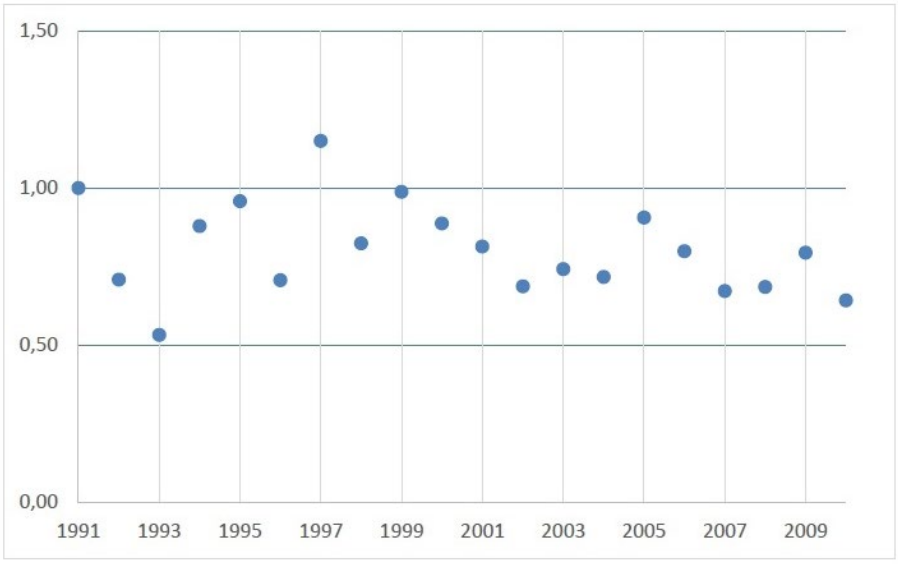
RER in aged patients



RR continue: 0.986 (0.970-§.003) p=0.123

FIGURE 1B: RER in aged patients (65-75 years) adjusted for age, sex, grade and treatment

RER in elderly patients



RR continue: 0.988 (0.971-1.004) p=0.150

FIGURE 1C: RER in elderly patients (>75 years) adjusted for age, sex, grade and treatment

Poster #025 3439834

MACHINE LEARNING TOOL SUCESSFULLY CLASSIFIES TREATMENT RESPONSE IN HIGH-GRADE OSTEOSARCOMA

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Objective: Osteosarcoma, the most common malignant pediatric bone tumor, remains dependent on systemic treatment largely unchanged in 30-years. We hypothesized that we could create a novel approach using machine learning to interpret chemotherapy response by combining 3-dimensional co-registration techniques using both advanced imaging and digital histology.

Methods: We enrolled patients with newly diagnosed appendicular high-grade osteosarcoma, to a single-center observational trial wherein patients completed advanced MRI (aMRI) sequences (diffusion weighted – DWI, and dynamic contrast enhanced – DCE) at the time of conventional MRI (cMRI) sequences (post contrast T1 fat suppression, T1 weighted and short inversion-time inversion recovery – STIR). Both aMRI and cMRI sequences were completed after 5-weeks of systemic therapy and immediately prior to surgical resection. Steps toward the comparison of MRI interpreted response to digital histology included: segmentation of tumor planes across MRI sequences, co-registration of histology and MRI planes of interest using 3-dimensional tumor molds, and control point mapping to a whole tumor histology image stitched from individual histology slides (previously reported) and pathologist annotated map representing areas of necrosis and viable tumor. Further steps included development of a machine learning tool to separate viable tumor from necrosis by statistical and Haralick texture features by conventional MRI and parameter maps calculated from advanced MRI sequences. Thereafter using FCM-clustering, percent necrosis was calculated for the plane of interest and whole tumor. Tumor necrosis calculated by MRI was compared to pathologist estimated necrosis and necrosis quantified from digitized histology using a previously described deep learning network. All patients or their parents signed informed consent for this study which was IRB approved at UT Southwestern Medical Center Dallas.

Results: To date 17 patients have been enrolled, average age 13-years, n=8 female. MRI data are described for 10-patients, n=2 still on study, n=2 withdrew, n=1 ineligible, n=2 inadequate pre-surgical imaging. Table 1 demonstrates the percent necrosis for each patient. Tumor necrosis calculated from cMRI+aMRI planes of interest yielded a measure of necrosis with an error of 3.5% +/-1.6% compared to pathologist estimated necrosis.

Conclusion: We have developed a machine learning tool that sucessfully calculates chemotherapy response for patients with high-grade osteosarcoma by MRI. We will continue to refine the machine learning tool and will work to generalize it to other childhood malignancies.

Table 1: Percent tumor necrosis calculated by pathologist, deep learner from digital histology and machine learner from pre-surgery MRI scans

Patient ID	Pathologist estimated necrosis	Deep Learner estimated necrosis	FCM estimated necrosis on MRI plane of interest (cMRI)	FCM estimated necrosis on whole tumor (cMRI)	FCM estimated necrosis on MRI plane of interest (cMRI+aMRI)	FCM estimated necrosis on whole tumor (cMRI+aMRI)
1	25	31	11	10	.	.
2	99	88	99	99	.	.
3	95	93	88	74	92	88
4	90	91	88	86	93	95
5	80	49	.	.	95	88
6	100	91	91	89	94	91
7	95	92	91	96	92	78
8	75	68	90	89	81	81
9	85	78	92	86	87	88
10	.	91	92	92	93	96
Mean	82	77	82	80	91	88

Poster #026 3440865

OUTCOME OF COMBINING RESECTION OF SARCOMA WITH INVOLVED BOWELS IN PATIENTS WITH PRIMARY RETROPERITONEAL LIPOSARCOMA

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Objective: Primary retroperitoneal liposarcoma(PRPLS) often develops with bowel involvement. Whether to resect the involved bowel aggressively during tumor resectional surgeries or preserve them as much remains conflict. This study aimed to analyze the outcome of primary retroperitoneal liposarcoma underwent resection surgeries of tumor combining with involved bowel.

Methods: Medical records of patients with primary retroperitoneal liposarcoma who were admitted to surgery in a referral sarcoma center from January 2015 through July 2019 were retrospectively reviewed. Data collected included demographics, operative outcome, pathological findings, and survival probabilities. PFS and OS were compared between pathological bowel infiltration positive and negative groups.

Results: A total of 24 patients (male 17) aged 54.8±11.5 years were included in this study, of which 6 cases underwent combining right hemicolectomy, 8 left hemicolectomy, 6 sigmoidectomy, 2 proctectomy, and 8 small bowel resection. Reasons for bowel resection were macroscopic infiltration (18), iatrogenic injuries (5) and ischemia (1) during adhesiolysis. Median operative time was 320 (interquartile range, IQR, 243-445) min and blood loss was 1150(IQR, 600-2000) ml. The postoperative morbidity was 37.5%(9/24). 2 had anastomotic fistula. There was no operative mortality. Final pathology disclosed 13 well differentiated liposarcoma (WDDLPS) and 11 dedifferentiated liposarcoma (DDLPS). 18/24 cases were confirmed with bowel infiltration pathologically. After an average of 25 months following up, 8 cases developed recurrences and 3 deceased. Two-year overall survival(OS) and progression free survival(PFS) probability were 91% and 70.8% respectively. Dedifferentiated liposarcoma as a pathological type was found as the only risk factor associated to poor PFS. There were no statistical differences of PFS and OS between bowel infiltration positive and negative groups.

Conclusion: Combining resection of PRPS with bowel was relatively safe with low morbidity, decreasing the tumor residue, which may get optimal local control in patients with DDLPS.

Risk factors associated to PFS in all patients

Variables	P Value	95% Confidence Interval
Age	0.832	0.908, 1.128
Gender	0.875	0.145, 5.180
Bowel infiltration microscopically	0.555	0.268, 11.622
Pathological type	0.042	1.089, 90.645
Bowel fistular	0.570	0.028, 7.219

Poster #027 3441221

A PHASE 1, MULTICENTER, OPEN-LABEL, FIRST-IN-HUMAN STUDY OF DS-6157A IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR

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Objective: Gastrointestinal stromal tumor (GIST) is a rare cancer of the digestive tract with limited treatment options. G protein-coupled receptor 20 (GPR20) is selectively and abundantly expressed in GIST; the expression of GPR20 is regulated by FOXF1 and ETV1—transcription factors that play critical roles in GIST initiation, proliferation, and survival. DS-6157a is an antibody-drug conjugate composed of a humanized anti-GPR20 IgG1 monoclonal antibody covalently conjugated to a drug-linker that releases its payload, DXd, upon internalization by cancer cells. DXd is an exatecan derivative that inhibits cell replication and induces apoptosis by inhibiting DNA topoisomerase I. DS-6157a inhibited the growth of GPR20-expressing GIST cells in vitro and inhibited tumor growth and induced tumor regression in GPR20-expressing GIST xenograft mouse models. The objective of this trial is to evaluate the safety, tolerability, and preliminary antitumor activity of DS-6157a in patients with advanced GIST.

Methods: This is a phase 1, multicenter, open-label, first-in-human study of DS-6157a in patients with advanced GIST (NCT04276415). This study has 2 parts: dose escalation (part 1) and dose expansion (part 2). The primary objectives of part 1 are to assess the safety and tolerability of DS-6157a and determine the maximum tolerated dose and/or recommended dose for expansion (RDE). The primary objectives of part 2 are to evaluate the safety, tolerability, and efficacy of DS-6157a at the RDE. The secondary objectives of part 1 and part 2 include the pharmacokinetic characterization of DS-6157a, measurement of the total anti-GPR20 antibody and drug component in plasma, and assessment of the incidence of anti-drug antibodies against DS-6157a. Key inclusion criteria include age ≥ 20 years (Japan) or ≥ 18 years (other countries), an *Eastern Cooperative Oncology Group* performance status of 0 or 1, and ≥ 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1. Key exclusion criteria include concomitant treatment with any medication that is classified as having a known risk of torsades de pointes, a documented history of noninfectious interstitial lung disease (ILD)/pneumonitis that required corticosteroids, current or suspected ILD/pneumonitis, and clinically significant pulmonary compromise or requirement for supplemental oxygen. Part 1 includes patients with GIST who meet 1 of the following criteria (n ≈ 40): (a) are not candidates for imatinib (IM) or curative intent surgical treatment; (b) (US only) progressed on or are intolerant of IM and ≥ 1 post-IM treatment or are not candidates for post-IM standard of care treatment; (c) (Japan only) received all existing standard-of-care treatments or are not candidates for ≥ 1 available post-IM standard-of-care treatment. Part 2 consists of 2 cohorts: cohort 1 (n ≈ 30) includes patients who have progressed on or are intolerant of IM and ≥ 1 post-IM therapy; cohort 2 (n ≈ 30) includes patients who have progressed on IM and have not received a post-IM therapy. Enrollment in part 1 will be regardless of GPR20 expression. If part 1 indicates a correlation between GPR20 expression and safety/efficacy, biomarker assessments may be considered in patient selection for part 2. The starting dose of DS-6157a for part 1 is 1.6 mg/kg administered intravenously on day 1 of each 21-day cycle. Dose escalation of DS-6157a will be guided by a Bayesian logistic regression model following the escalation with overdose control. Approximately 100 patients are expected to be enrolled in this study at centers worldwide, including in the United States and Japan.

Results: This is a trial in progress; no results are available.

Conclusion: This is a trial in progress; no conclusions are available.

Poster #028 3441532

DUAL-ENERGY CT AS A QUANTITATIVE RESPONSE PARAMETER IN PATIENTS WITH GIST UNDERGOING TARGETED THERAPY – A PROSPECTIVE MULTI-CENTER TRIAL

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Objective: Though RECIST 1.1 still remains the reference standard in clinical trials on GIST patients, it does not account for characteristic tyrosin kinase inhibitor (TKI) therapy related response changes, such as hemorrhage, myxoid degeneration, or transient increase in tumor size. TKI specific tumor metrics have been proposed, such as the modified Choi criteria (mChoi) and the Vascular Tumor Burden (VTB), which attempt to overcome some of the limitations of RECIST 1.1, but lack prospective validation. Contrast-enhanced dual energy CT (DECT) permits the exact quantification of vital tumor portions from other tumor portions by characterizing the total amount of intra-tumoral iodine. The purpose of this study was to determine, if DECT Vital iodine Tumor Burden (ViTB) allows reliable response assessment in patients with GIST compared to established CT criteria.

Methods: From 1/2014-6/2018, 128 patients (median age 58.4 years [30-77 years]) with biopsy proven GIST were entered in this prospective, multi-center trial. All patients were treated with TKIs for primary (n=21) or metastatic (n=107) disease and underwent a pre-treatment and follow-up DECT examine. Response assessment was performed according to RECIST 1.1, mChoi, VTB and DECT ViTB. DECT ViTB used the same cut points for percentage change as RECIST 1.1. Patients were observed for a minimum of 18 months (median 32 months). Progression-free survival (PFS) in responders (CR, PR and SD) and non-responders (PD) according to each response criteria was compared by using the Cox proportional hazard ratio (HR) and the Harrell c-Indices.

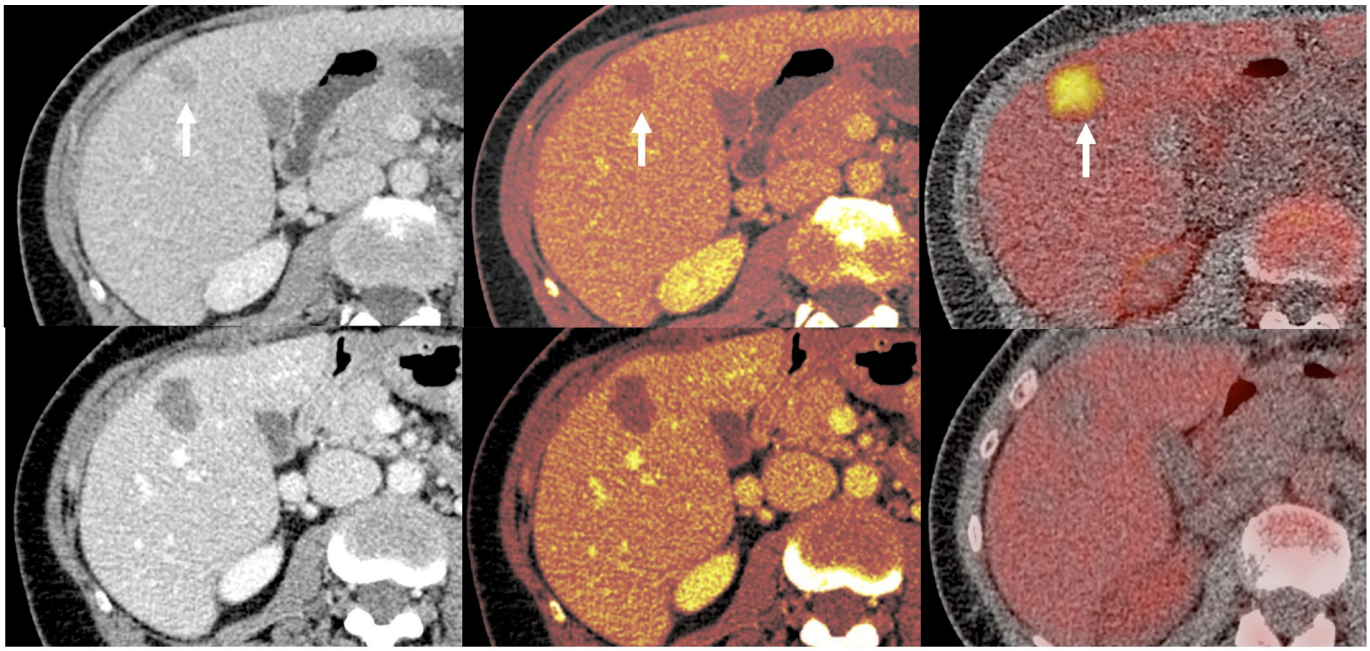
Results: The median PFS was significantly different between non-responders and responders for all response metrics and comparable among the RECIST1.1 (HR=3.6; 95%CI: 2.4-5.9; p<.001) and mChoi criteria (HR=2.6; 95%CI: 1.7–4.2; p<.001). DECT ViTB non-responders were 15 times more likely to experience progression of disease (HR=15.0; 95%CI: 8.2-26.0; p<.001) than responders. DECT ViTB had a significant superior response discrimination ability if compared to RECIST 1.1, mChoi and VTB (c-Index: 0.77 compared to 0.62-0.70; all p<0.001).

Conclusion: The ViTB assessed by DECT provides a reliable, consistent method to quantify response changes to TKI therapy in GIST. ViTB outperformed current CT response criteria such as RECIST 1.1, mChoi and VTB. As DECT systems are becoming available on a broader range, the method could be used in clinical trials, and potentially expanded to other tumor entities treated with TKIs.

TABLE:

Response Metrics	N	Median [d]	HR	P-Value	Harrell's C-Index
RECIST1.1 criteria					
Responder	97	376 [85-1264]	3.6 (2.4 - 5.9)	<0.001*	0.63
Non-Responder	31	104 [63-462]			
mChoi criteria					
Responder	85	385 [85-1275]	2.7 (1.7 – 4.2)	<0.001*	0.62
Non-Responder	43	123 [64-655]			
VTB criteria					
Responder	83	425 [123-1287]	3.2 (3.8 – 8.0)	<0.001*	0.70
Non-Responder	45	97 [63-361]			
DECT ViTB criteria					
Responder	75	526 [157-1376]	15.0 (8.2 - 26.0)	<0.001*	0.77
Non-Responder	53	104 [63-248]			

Figure – 49-year old female GIST patient with a new metastatic liver lesion and known exon 11 mutation undergoing new Imatinib 400 mg therapy. As indicated by the white arrow a target lesion selection match was performed on the baseline blended CT images (A), DECT overly images (B) and PET-CT images (C) in the transversal plane. The tumor metrics longest diameter according to RECIST 1.1. (D) and attenuation according to the Choi criteria (D) indicated progressive disease (PD) at follow-up suggesting a change in therapy. Vascular Tumor Burden (VTB) (D), DECT Vital iodine Tumor Burden (ViTB) (E) correctly identified early partial response (PR) of the target lesion on the initial follow-up examination as indicated by the follow-up PET CT (F) with a decrease in metabolic lesion activity below the liver background, indicating size pseudo-progression.



Metric	**TP_0**	**TP_1**	**Criteria**	**Response**
Max. length	14 mm	24 mm	*RECIST 1.1*	+71% = PD
Mean attenuation	70 HU	51 HU	*mChoi*	+71%/-27% = PD
Area	2.1 cm^2	1.6 cm^2	*VTB*	-25% = PR
Vital volume	1.9 mg	0.7 mg	*DECT ViTB*	-73% = PR

Poster #029 3441865

PROGNOSES OF SUPERFICIAL SOFT TISSUE SARCOMA: THE IMPORTANCE OF FASCIA-TUMOR RELATIONSHIP ON MRI

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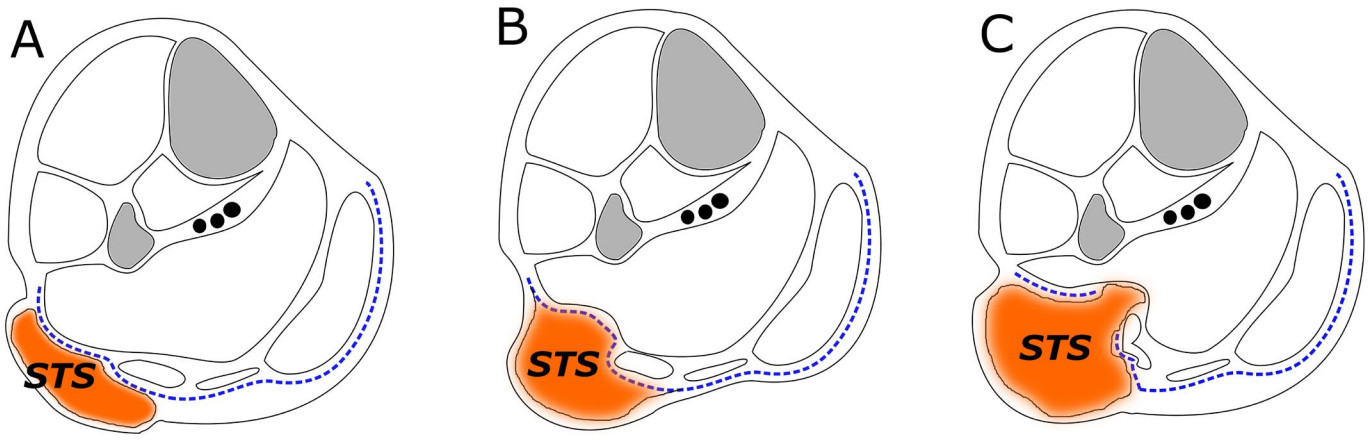
Objective: Superficial soft-tissue sarcoma (S-STS) has been reported to have more favorable prognoses than deep-seated STS. However, for some patients, poor prognoses have been observed and there is a need for better prognostication. The deep peripheral fascia lies in the border of the S-STS and can be consistently detected using magnetic resonance imaging (MRI). The relationship of the subcutaneous tumor with the fascia on MRI scan was reported to be useful in classifying the tumor as benign or malignant; this in turn, may reflect the biological aggressiveness of STS. This study was performed to evaluate the oncologic outcomes and to identify the prognostic factors of S-STS by focusing on the relationship of S-STS with the underlying fascia on MRI.

Methods: We retrospectively reviewed data on 253 patients who underwent resection of localized S-STS. Potential factors that might influence the oncologic outcomes were identified. The fascia-tumor relationship on MRI was classified into three groups: no fascial contact group (n=46), fascial contact group (n=77), and fascial invasion group (n=84) (Fig.1).

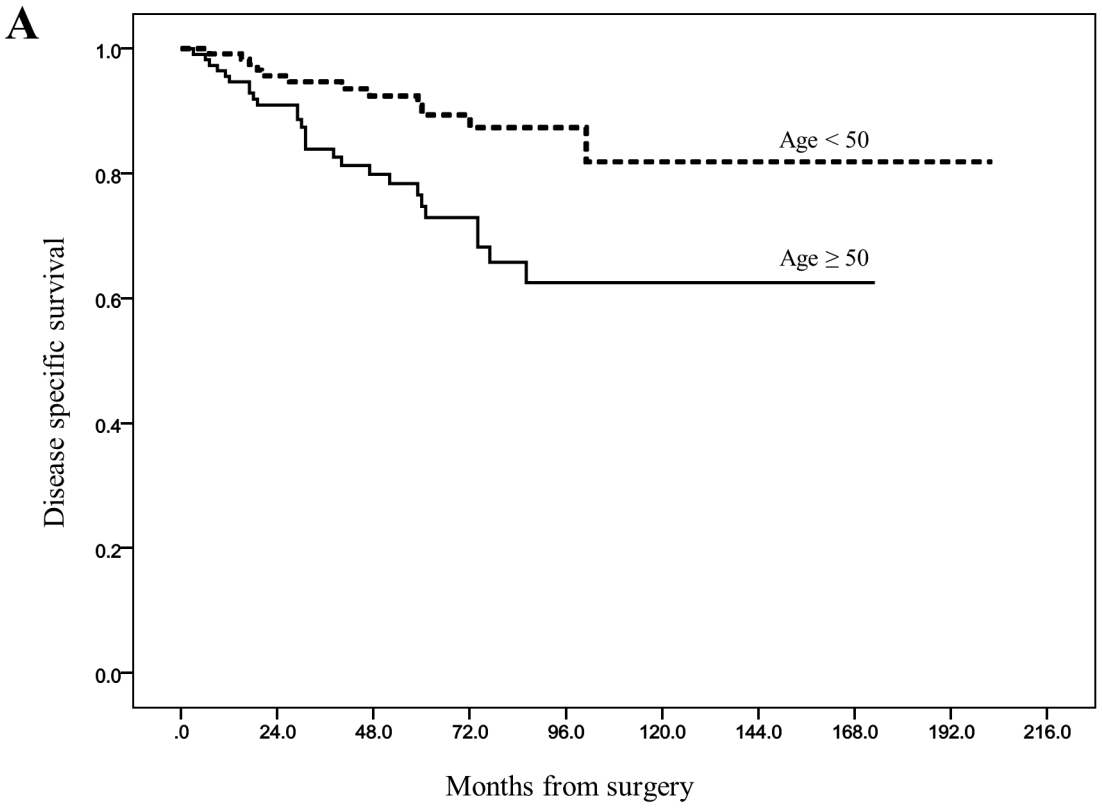
Results: Overall, 39 patients (16.5%) died due to S-STS; the 5- and 10-year survival rates were 82.6±2.9% and 73.2±4.5%, respectively. Fascial invasion detected on MRI scans (OR=2.190, p=0.034) and advanced age (OR=2.408, p=0.034) were found to be independent factors for worse overall survival (Fig.2). The fascia-tumor relationship on MRI scan was not associated with local recurrence of S-STS.

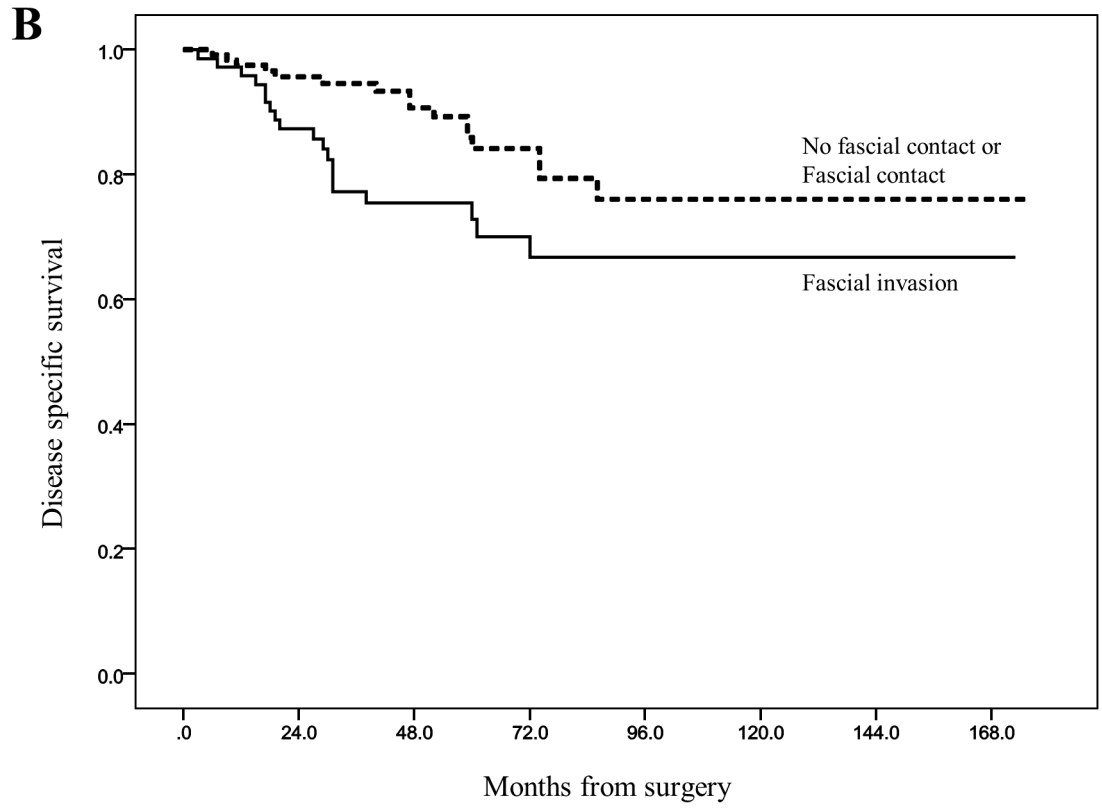
Conclusion: The fascia-tumor relationship on MRI scan reflects the biological aggressiveness of S-STS and can serve as a prognostic factor.

Cross-section of the fascia-tumor relationship in the lower leg. The mass labeled STS is soft tissue sarcoma and the dotted line is the fascia. (A) No fascial contact; (B) fascial contact, the mass comes in contact with the fascia, but it does not infiltrate across the fascia; and (C) fascial invasion, the mass penetrates through the fascia and spreads beyond.



Kaplan–Meier survival curve representing disease specific survival of superficial soft-tissue sarcoma based on (A) age and (B) fascia-tumor relationship on MRI scan.





Poster #030 3442000

OUTCOME OF CLINICAL GENETIC TESTING IN PATIENTS WITH SARCOMA

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Objective: The understanding of genetic predisposition in sarcoma is evolving rapidly in conjunction with increased utilization of tumor genomic testing. We sought to describe the characteristics of sarcoma patients referred for clinical genetic testing and to determine the prevalence of pathogenic/likely pathogenic germline variants.

Methods: We performed retrospective chart reviews of individuals with sarcoma who were referred and underwent genetic evaluation at the Michigan Medicine Cancer Genetics Clinic between December 2006 and January 2020. Data regarding medical and family history, cancer phenotype, and results of germline genetic testing, if applicable, were obtained. Descriptive analyses were performed to assess the prevalence of germline variants classified as pathogenic/likely pathogenic according to American College of Medical Genetics (ACMG) criteria. Associations with clinical factors and reasons for recurrence were tested for using Fisher's exact test or Wilcoxon rank-sum test, depending on the type of the clinical factor.

Results: Seventy-two patients with sarcoma underwent clinical genetic evaluation during this 13-year period. Mean age at the time of visit was 44 years (SD 17.1 years, range 2-80 years), and 34 patients (47.2%) were male. The most common reasons for referral included personal history of multiple malignancies (n=42, 58.3%), first-degree relative with a history of malignancy (n=39, 54.2%) and young age at sarcoma diagnosis (age ≤18, n=14, 19.4%). Twenty-nine patients (40.3%) had both a history of multiple malignancies and a first-degree relative with a history of malignancy. Six patients (8.3%) had a first-degree relative with sarcoma. Of the 66 patients who underwent clinical germline sequencing, 31 patients (46.9%) had a pathogenic or likely pathogenic germline variant associated with a known cancer predisposition syndrome. Germline variants included *TP53* (n=10, 15.2%), *MSH2* (n=4, 6.1%), *FLNC* (n=2, 3.0%), *ATM* (n=2, 3.0%) and one each (1.5%) of *CDKN2A, FH, MUTYH, PTEN, RB1, SDHB, NTHL-1, SMAD4, BARD1, PMS2, POLE, POT1*. There was no statistical significance between young age at diagnosis, history of personal malignancies, first-degree relative with sarcoma, first-degree relative with multiple malignancies, or multiple first-degree relatives with malignancy and presence of a pathogenic/likely pathogenic germline variant.

Conclusion: In this study, nearly half of patients with sarcoma referred for cancer genetic testing were found to carry a pathogenic/likely pathogenic germline variant associated with hereditary predisposition to cancer. Given the relatively high prevalence of germline findings, germline multigene panel testing should be considered in individuals with sarcoma. As multiple variants were identified extending beyond *TP53*, germline multigene panel testing evaluating syndromes in addition to Li Fraumeni should be considered. Our study did not capture patients who had known germline findings and were not referred to clinic or those who did not attend a genetics consultation even if referred. Our study was limited by small sample size and highlights the need for further understanding as to the prevalence of germline mutations in sarcoma patients and to the predictive factors of positive results.

Sarcoma subtypes, germline variants, age at diagnosis and reason for referral

Sarcoma subtype	Germline Variant	Age at diagnosis (years)	Reason for referral
Osteosarcoma	ATM	87	GP, FH1
	CDKN2A	13	Age, MFHM
	FLNC (2)	16, 23	Age, GP, FH1
	POT1	28	Age
Leiomyosarcoma	FH	25	Age, FHSarc
	MUTYH	52	PMH2, MFHM
	RB1	47	PMH2, MFHM
	TP53 (4)	39, 41, 54, 61	PMH2, FHM, MFHM
	SDHB	60	FH1
Liposarcoma	SMAD4	41	FHSarc, FHM
Pleomorphic	ATM	66	PMH2, FH1
	MSH2	41	FHM, MFHM
	TP53 (4)	23, 29, 32, 65	PMH1, FH, PMH2
Angiosarcoma	MSH2	64	PMH2, FHM, MFHM
Chondrosarcoma	NTHL1	40	PMH1, FH1
Rhabdomyosarcoma	BARD1	14	Age, PMH1
	TP53 (2)	1, 7	Age, PMH1
Epithelioid	PMS2	39	MFHM
Spindle cell	MSH2	49	PMH2, MFHM
	POLE	56	FH1
Fibrosarcoma	TP53	33	PMH1, FHSarc, MFHM
Myxofibrosarcoma	MSH2	62	PMH1, MFHM
Juvenile dermatofibrosarcoma protuberans	PTEN	7	PMH1, FH1

Age: young age at diagnosis
GP: known genetic predisposition in a first-degree relative (FDR)
PMH1: past medical history of one malignancy in addition to sarcoma
PMH2: past medical history of two or more malignancies in addition to sarcoma
FHSarc: family history of FDR with sarcoma
FH1: family history of FDR with any type of malignancy
FHM: family history of FDR with multiple personal malignancies
MFHM: family history of multiple FDR with one or more personal malignancies

Poster #031 3442052

VARIANCE BETWEEN EXPERTS AND COMMUNITY PRACTITIONERS IN TREATING SOFT TISSUE SARCOMAS: ANALYSIS OF AN ONLINE DECISION SUPPORT TOOL

Ryan P. Topping[1], *Vicki L. Keedy*[2], *Shreyaskumar Patel*[3], *Richard F. Riedel*[4], *Brian A. Van Tine*[5], *Timothy A. Quill*[1], *William D. Tap*[6]
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Objective: Soft tissue sarcomas (STSs) are rare cancers comprising > 50 histologic subtypes, each of which has unique management considerations. Current clinical practice guidelines note numerous targeted and chemotherapy options for patients with advanced STSs but generally lack specificity in providing recommendations for individual STS subtypes. As such, it is recommended that patients with STSs be treated at high-volume centers; however, this is not always possible.

We developed an online treatment decision support tool designed to provide oncology healthcare providers (HCPs) with case-specific treatment recommendations from 5 STS experts. Here, we report an analysis of cases entered into the tool by HCPs, comparing their planned treatment with expert recommendations and assessing the impact of those recommendations on intended HCP treatment decisions.

Methods: In February 2019, 5 STS experts provided treatment recommendations for 272 distinct STS case scenarios that were defined by numerous key factors, including STS subtype, the presence of symptomatic disease, and previous treatment. Seven of the most common chemotherapy-sensitive histologic STS subtypes were selected for the tool (Figure). To use the tool, HCPs entered their patients' information and their intended treatment plan; expert recommendations for that specific patient scenario were then provided, followed by a survey designed to determine whether the recommendations had changed the HCP's intended treatment. For this analysis, cases entered into the tool by HCPs were compared with expert recommendations for numerous scenarios, and responses to the post-recommendation survey were assessed.

Results: Between April 2019 and May 2020, 605 cases were entered into the tool by 349 HCPs (85% of cases by physicians). 61% of respondents reported treating ≤ 10 patients with STSs per year, and 62% sought recommendations for a specific patient. Notably, cases of leiomyosarcoma or liposarcoma were most frequently entered into the tool (Figure); however, a significant number of cases were entered for relatively rarer subtypes, including synovial sarcoma and angiosarcoma.

Substantial variance was observed for a variety of case scenarios when the planned treatment of HCPs was compared with expert recommendations (Table). For example, for patients with advanced leiomyosarcoma potentially requiring more aggressive first-line therapy, the expert panel selected doxorubicin plus dacarbazine or ifosfamide for 83% of cases, while HCPs planned to use one of these regimens for only 40% of cases. Overall, after reviewing expert recommendations for their cases, 66% of HCPs whose planned treatment differed from the experts indicated that they would change their treatment based on panel recommendations.

Notably, a lack of consensus was observed among experts for numerous case scenarios. For example, for cases in which a patient with unresectable/metastatic angiosarcoma required first-line systemic therapy, the experts favored gemcitabine plus docetaxel, gemcitabine plus paclitaxel, or paclitaxel alone with similar frequency.

Conclusion: Analysis of data from an online treatment decision support tool suggested differences in how experts and community providers manage patients with advanced STSs of varied histologic subtypes. Expert recommendations in the tool changed the intended treatment plan of many HCPs, suggesting that online treatment decision tools that provide customized, patient-specific expert advice may increase implementation of optimal therapeutic decisions for advanced STSs. A full analysis of cases entered into the tool will be presented.

Figure. Cases Entered into the Tool According to Histologic Subtype (N = 605).

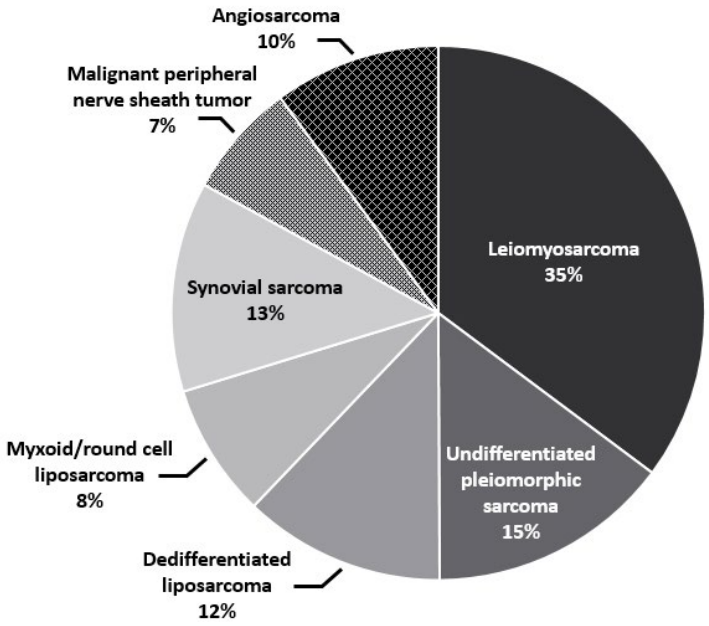

Table. HCP and Expert Treatment Choices for Select Case Scenarios of Fit Patients With Unresectable/Metastatic Disease.

Case Scenario	Foremost Expert Tx Recommendations, %	HCPs Selecting Foremost Expert Tx Recommendation, % (n/N)
Leiomyosarcoma		
No previous systemic treatment		
▪ Potentially requiring more aggressive treatment*	Dox + dacarbazine, 43 Dox + ifosfamide, 40	8 (8/98) 32 (31/98)
▪ Asymptomatic disease	Dox, 60	30 (9/30)
Previous first-line systemic treatment		
▪ Previous anthracycline-based therapy, poor response†	Gem-based therapy, 93	39 (19/49)
▪ Previous gem-based regimen, poor response†	Dox + dacarbazine, 60‡	10 (1/10)
Synovial sarcoma		
No previous systemic treatment		
▪ Potentially requiring more aggressive treatment*	Dox + ifosfamide, 93	53 (16/30)
▪ Asymptomatic disease	Dox + ifosfamide, 60	40 (2/5)
Previous anthracycline ± ifosfamide with poor response†	High-dose ifosfamide, 60	6 (1/15)
Angiosarcoma		
No previous systemic treatment	Gem + docetaxel, 30 Paclitaxel, 30 Gem + paclitaxel, 25	5 (2/37) 25 (9/37) 5 (2/37)
Myxoid/round cell liposarcoma		
No previous systemic treatment	Dox + ifosfamide, 85	33 (9/27)
Previous anthracycline ± ifosfamide with poor response†	Trabectedin, 60	25 (2/8)

*Symptomatic disease/need for rapid palliation or locally advanced unresectable disease with potential for conversion to resectable disease. †No/minor PFS response. ‡Choices partially dependent on presence of symptomatic disease/need for rapid palliation.
Dox, doxorubicin; Gem, gemcitabine; Tx, treatment.

Poster #032 3442782

ANTI-TUMOR EFFECT OF LAT1 INHIBITOR ON CLEAR CELL SARCOMA CELL LINE

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[2]*Orthopaedic Surgery, Hyogo Cancer Center, Akashi, JAPAN*

Objective: Clear cell sarcoma (CCS) is a rare and poor-prognostic malignant soft tissue tumor which occurs primarily in the extremities of young adults. The standard treatment of CCS is wide surgical resection, and neither common chemotherapy nor radiotherapy is effective.

An amino acid transporter, L-type Amino Acid Transporter1 (LAT1) is specifically expressed in the cell membrane of various malignant tumors such as prostate, breast, gastric, lung and pancreatic cancers, and has been shown to be involved in the uptake of essential amino acids, which are necessary for tumor cell growth. We have previously presented that LAT1 is highly expressed in human clear cell sarcoma (CCS) cell lines, therefore we consider that LAT1 could be a therapeutic target for tumor cell metabolism in CCS.

In this *in vitro* study, we investigated the antitumor effects of LAT1 inhibition in a human CCS cells.

Methods: We employed a human CCS cell line MP-CC-SY, and a selective LAT1 inhibitor, JPH203 (J-Pharma, Japan) in this study. To investigate the metabolic change by LAT1 inhibition in the CCS cells, we performed GC/MS-based metabolomic analysis after JPH203 treatment. The effect of JPH203 alone or in combination with doxorubicin (DXR) on the cell viability was examined using WST assay, and the potency of the combination was quantified with CompuSyn Software (ComboSyn, USA). Effects of LAT1 inhibition on apoptotic activity was assessed by Annexin A5/PI staining using a flow cytometry, and by Caspase-Glo 3/7 and 8 Assay kit.

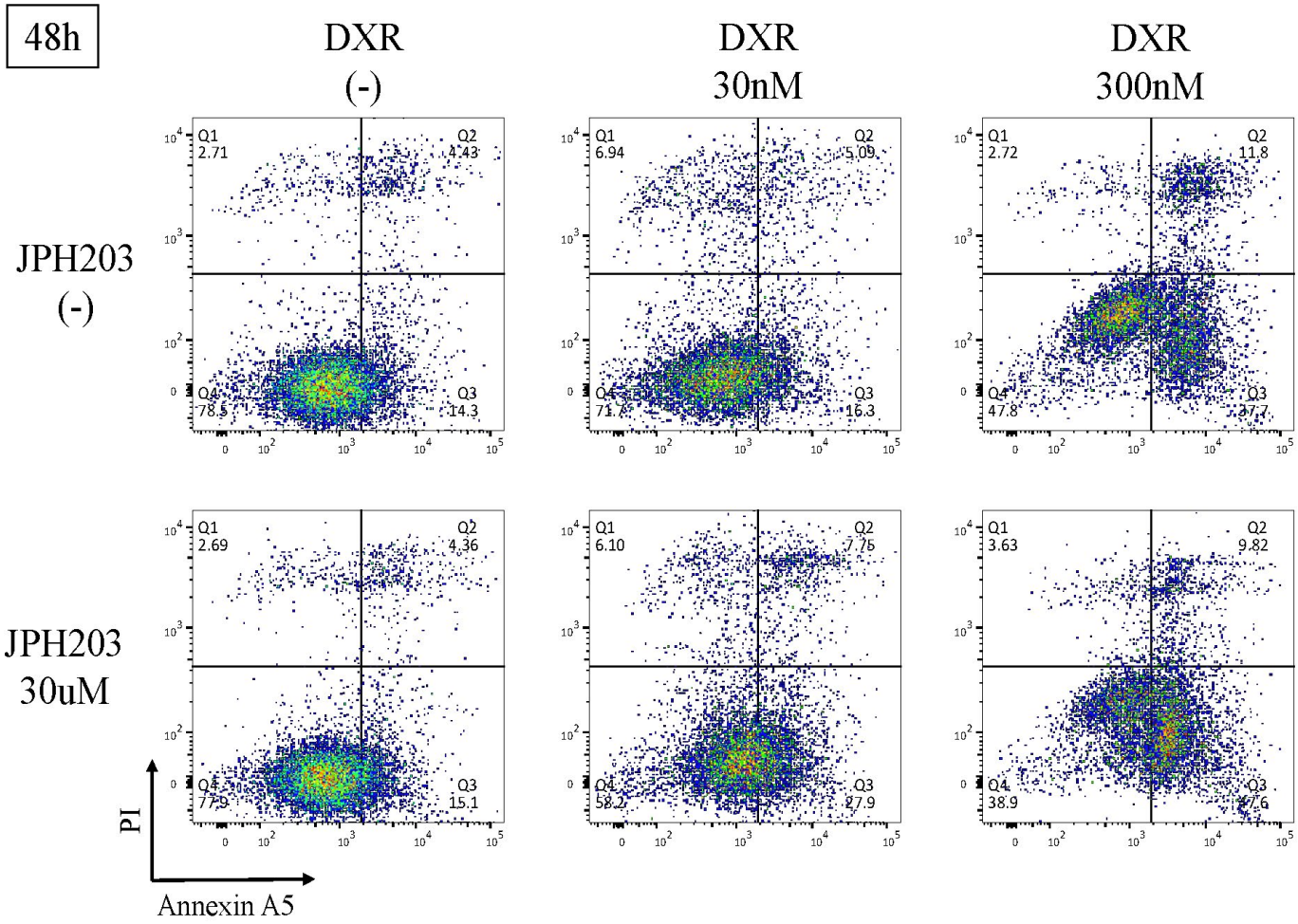
Results: In the metabolomic analysis, the significant decrease in essential amino acids including leucine (41.5% compared to control) was observed in the cells after 48 hours of 30μM JPH203 treatment compared to the control. In WST assays, JPH203 alone showed a slight inhibitory effect on CCS cell growth, while combination with DXR showed a strong synergistic effect at 48 hours after treatment (Combination Index; 0.39).

Annexin A5/PI staining proved that the number of apoptotic cells were significantly increased in the cells with JPH203 (30μM) and DXR (300nM) treatment (Fig. 1). The caspase activities were not increased by JPH203-alone treatment. However, in combination with DXR, JPH203 sensitized the cytotoxic effect of DXR (Fig.2).

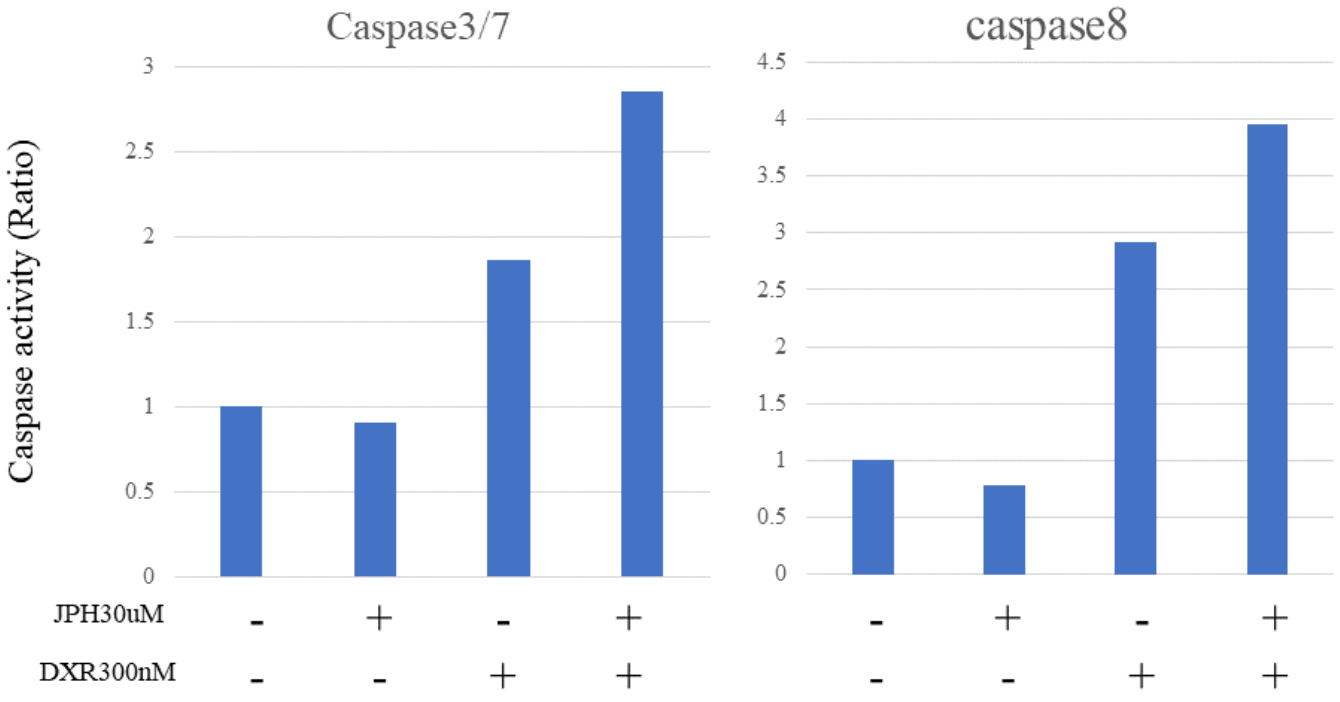
Conclusion: This is the first *in vitro* study to show the effects of LAT1 inhibition in CCS cells. In this study, metabolomic analysis revealed that JPH203 treatment could inhibit leucine uptake and sensitized the cytotoxic effects of DXR in CCS cells. Previous reports suggest that leucine is one of the most potent activators of mTORC1 and that cancer cells rely on constitutively active mTORC1 signaling. Therefore, the findings in this study indicate that a limited supply of leucine by LAT1 inhibition may cause mTORC1 down-regulation, and resulting in enhanced apoptotic effect of DXR. Further investigation is necessary to establish the effects of LAT1 inhibition by JPH203 on mTORC1 in CCS.

In conclusion, LAT1 inhibition by JPH203 led to apoptotic cell death by inducing the intracellular depletion of essential amino acids and increased DXR sensitivity in CCS cells. LAT1 may be a potent therapeutic target for CCS.

Annexin A5/PI staining in CCS cells after JPH203, DXR and their combination treatment.



Caspase 3/7 and 8 activities in CCS cells after JPH203, DXR and their combination treatment.



Poster #033 3443018

OPPORTUNISTIC MUSCLE MEASUREMENTS ON STAGING CHEST CT FOR EXTREMITY AND TRUNCAL SOFT TISSUE SARCOMA ARE ASSOCIATED WITH SURVIVAL

Eileen Phan[3], *Steven W. Thorpe*[1], *Felix S. Wong*[4], *Sandra Taylor*[5], *Augustine M. Saiz*[8], *Robert J. Canter*[6], *Leon Lenchik*[7], *R L. Randall*[1], *Robert Boutin*[2]

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Objective: CT measurements of sarcopenia, a proposed biomarker associated with survival prognosis in various cancers, has typically been evaluated at the L3 vertebral level. However, staging and surveillance imaging for patients with extremity and truncal soft tissue sarcoma (STS) often only includes chest CT scans which precludes evaluation muscle metrics at L3. Therefore, we sought to evaluate muscle metrics at T12 on standard staging chest CT scans and to determine if these metrics are prognostic of overall and event-free survival in patients with STS.

Methods: Using CPT codes for surgical resection of extremity and trunk sarcoma, baseline chest CTs from 2004-2017 were identified in 89 patients with grade 2 or 3 STS (53 M, 36 F; 58.5±19.0 years old, follow up 37.4±27.1 months) and reviewed on PACS at T12 for skeletal muscle density (SMD), a measure of muscle quality) and skeletal muscle index (SMI), a measure of muscle size. Muscle metrics were calculated by manually outlining the paravertebral muscles at T12 for SMD (measured in Hounsfield units, HU) and cross-sectional area (measured in cm^2) as shown in **Figure I.** Left and right paravertebral muscles were averaged in each patient. Muscle adiposity was evaluated based on CT density of the skeletal muscle, where lower SMD (HU) represents greater fat content within the muscle.

Results: Overall survival was significantly related to SMD (HR 0.61 [0.43, 0.86]) with increased survival associated with increased SMD even after adjusting for age (HR 0.65 [0.42, 0.98]). **Figure II** shows Kaplan-Meier curves for each muscle metric. Consistent with the proportional hazard modeling, KM curves demonstrated overall survival was greatest for patients with higher values ($Z \geq 1$) one standard deviation or greater above the mean for SMD but with no apparent relationship for SMI.

Like overall survival, event free survival increased with SMD but did not significantly relate to SMI. Adjusting for age widened confidence intervals, so the potential independent effect of SMD on event-free survival could not be determined. Kaplan-Meier analysis demonstrated a similar relationship between SMD and event-free survival higher values ($Z \geq 1$) representing improved EFS (**Figure III**).

Conclusion: Our study is the first to show that muscle quality (i.e., SMD) on chest CTs obtained for routine staging is a significant predictor of survival in patients with STS. We did not find any significant association between paravertebral muscle quantity (i.e., SMI) at T12 and survival in patients with STS, mirroring the results of previous studies evaluating psoas SMI at L3 on CTs of the abdomen. Future studies are needed to confirm our findings that SMD on routine chest CT scans is an independent predictor of mortality in STS and investigate clinically relevant cut-off values that may aid in risk stratification (e.g., predict treatment failure during adjuvant therapy), contribute to personalized medical management, and ultimately optimize patient outcomes.

Figure I. CT images of right and left paravertebral muscle density (HU) and cross-sectional area (cm^2) using PACS viewing software.

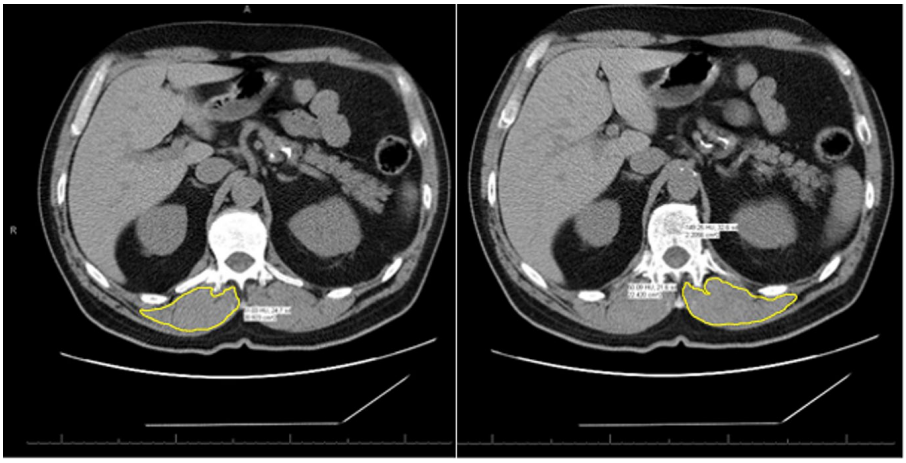


Figure II. Kaplan-Meier curves of overall survival relative to PACS by standardized deviations of SMD and SMI. Red is a standardized deviation or greater below the mean. Black is within one standardized deviation of the mean. Blue is a standardized deviation or greater above the mean.

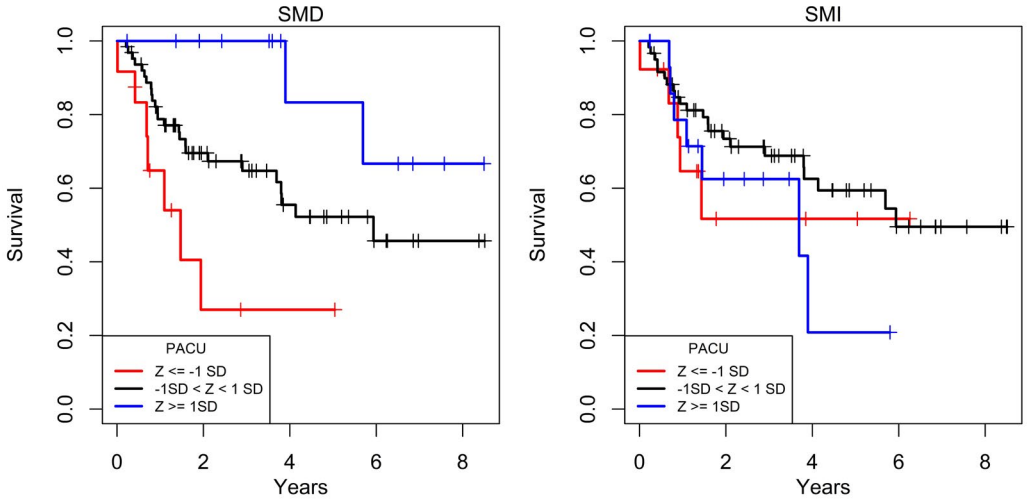
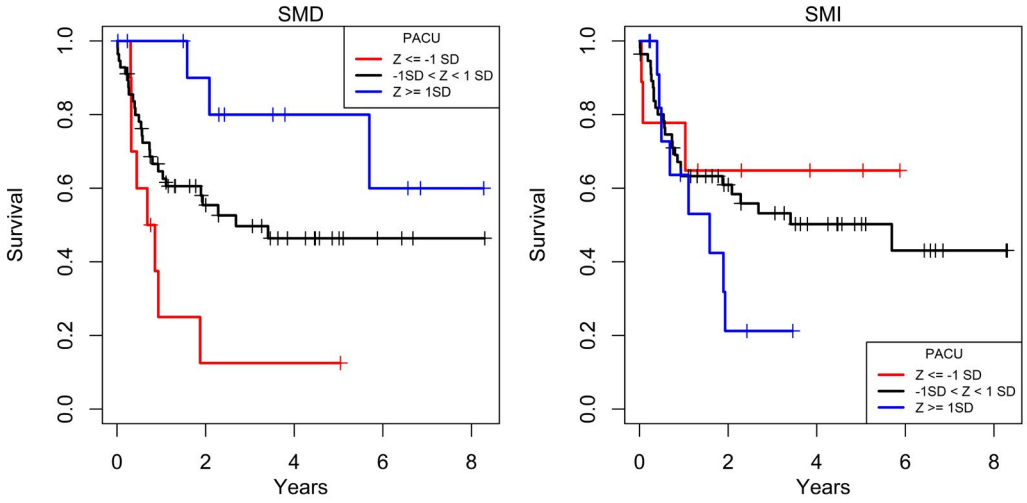


Figure IV. Kaplan-Meier curves of event-free survival relative to PACS by standardized deviations of SMD and SMI. Red is a standardized deviation or greater below the mean. Black is within one standardized deviation of the mean. Blue is a standardized deviation or greater above the mean.



Poster #034 3443510

IS SURGICAL RESECTION OF THE PRIMARY SITE ASSOCIATED WITH AN IMPROVED OVERALL SURVIVAL FOR PRIMARY MALIGNANT BONE TUMORS WITH METASTATIC DISEASE AT PRESENTATION?

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Objective: The management of primary malignant bone tumors in patients with metastatic disease at presentation remains a challenge. Although surgical resection has been a mainstay in the management of nonmetastatic malignant bone tumors, there is a lack of large-scale evidence based guidance on whether surgery of the primary site/tumor improves overall survival in malignant bone tumors with metastatic disease at presentation.

Methods: The 2004 to 2016 National Cancer Database (NCDB) was queried using International Classification of Diseases, 3rd Edition, topographical codes to identify patients with primary malignant bone tumors of the extremities (C40.0-C40.3, C40.8, and C40.9) and/or pelvis (C41.4). Histologic codes were used to categorize the tumors into the following groups: osteosarcomas, chondrosarcomas, and Ewing sarcomas. Patients whose tumors were classified as Stage I, II, or III based on American Joint Commission of Cancer guidelines were excluded. Only patients who presented with metastatic disease were included in the final study sample. The study sample was divided into two distinct groups: those who underwent surgical resection of the primary tumor and those who did not receive any operation for the primary tumor. Multivariate Cox regression analyses were used to assess whether undergoing surgical resection of the primary tumor was associated with improved overall survival, after controlling for differences in baseline demographics, tumor characteristics (grade, location, histologic type, and tumor size), and treatment patterns (resection of distant or regional metastatic sites, positive or negative surgical margins, and use of radiation therapy or chemotherapy). Additional sensitivity analyses, stratified by histologic type for osteosarcomas, chondrosarcomas, and Ewing sarcomas, were used to assess factors associated with overall survival for each tumor type.

Results: A total of 2288 patients with primary malignant bone tumors (1121 osteosarcomas, 345 chondrosarcomas, and 822 Ewing sarcomas) with metastatic disease at presentation were included, of whom 46% (1053 of 2288) underwent surgical resection of the primary site. After controlling for differences in baseline demographics, tumor characteristics, and treatment patterns, we found that surgical resection of the primary site was associated with reduced overall mortality compared with those who did not have a resection of the primary site (hazard ratio 0.42 [95% confidence interval 0.36 to 0.49]; $p < 0.001$). Resection of metastases was not associated with overall survival for the entire cohort (HR 0.92 [95% CI 0.81 to 1.05]; $p = 0.235$). Among other factors, in the stratified analysis, radiation therapy was associated with improved overall survival for patients with Ewing sarcoma (HR 0.71 [95% CI 0.57 to 0.88]; $p = 0.002$) but not for those with osteosarcoma (HR 1.14 [95% CI 0.91 to 1.43]; $p = 0.643$) or chondrosarcoma (HR 1.0 [95 % CI 0.78 to 1.50]; $p = 0.643$). Chemotherapy was associated with improved overall survival for those with osteosarcoma (HR 0.50 [95% CI 0.39 to 0.64]; $p < 0.001$) and those with chondrosarcoma (HR 0.62 [95% CI 0.45 to 0.85]; $p = 0.003$) but not those with Ewing sarcoma (HR 0.7 [95% CI 0.46 to 1.35]; $p = 0.385$).

Conclusion: Surgical resection of the primary site was associated with an overall survival advantage in patients with primary malignant bone tumors who presented with metastatic disease. Further research, using more detailed data on metastatic sites (such as, size, location, number, and treatment), chemotherapy regimen and location of radiation (primary or metastatic site) is warranted to better understand which patients will have improved overall survival and/or a benefit in the quality of life from resecting their primary malignant tumor if they present with metastatic disease at diagnosis.

Poster #035 3443839

CRYOABLATION: AN EFFECTIVE AND SAFE OPTION IN THE TREATMENT ALGORITHM OF EXTRA-ABDOMINAL DESMOID TUMORS?

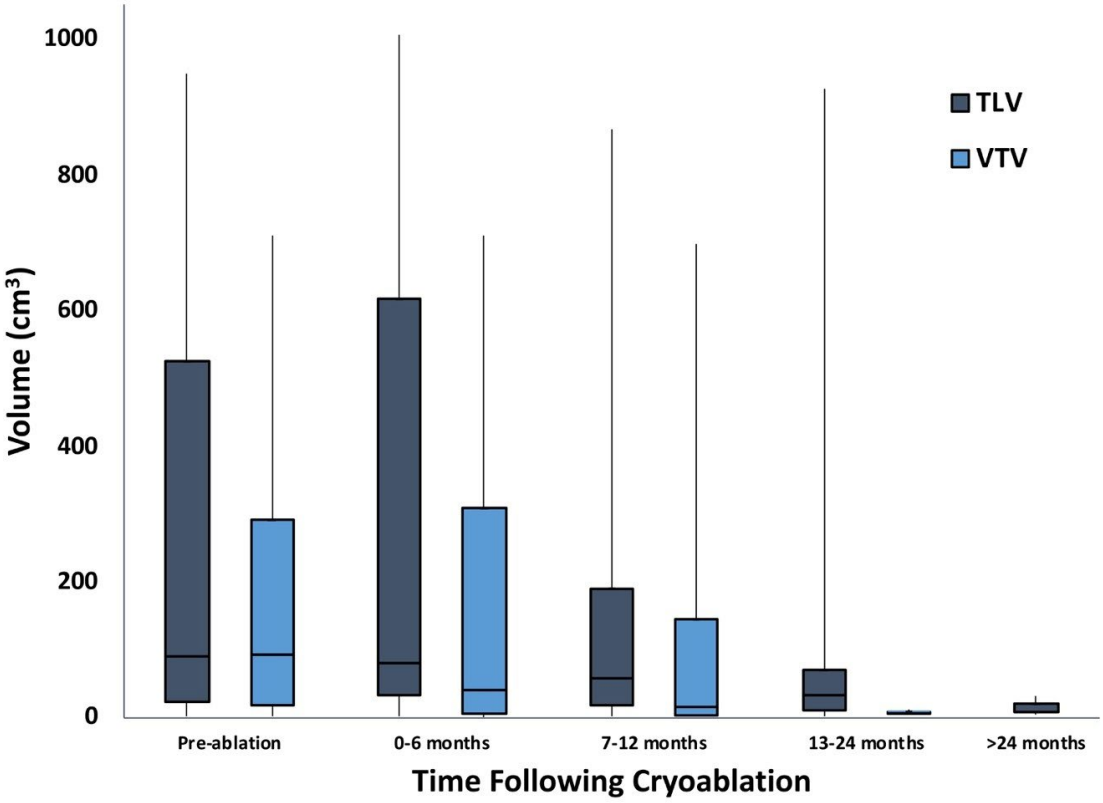
Yet Yen Yan[1], *Paul Mallinson*[1], *Peter Munk*[1], *John P. Walsh*[1], *Paul Clarkson*[2], *Prem Jayaram*[1], *Manraj Heran*[1], *Hugue Ouellette*[1], *Christine Simmons*[2]
[1]*Vancouver General Hospital, Vancouver, British Columbia, CANADA;*
[2]*BC Cancer Agency, Vancouver, British Columbia, CANADA*

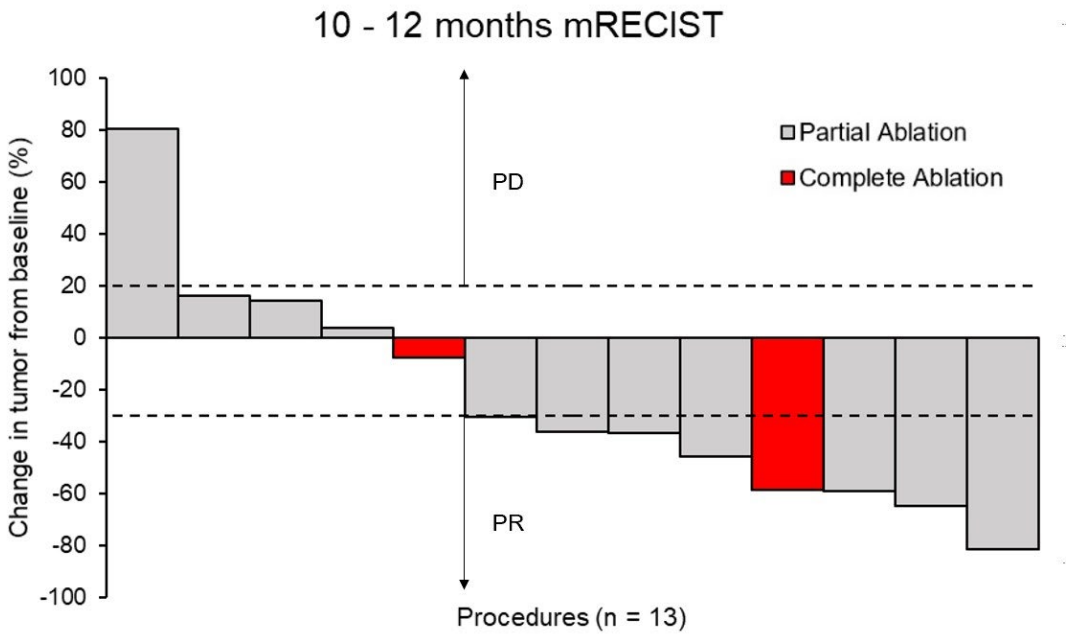
Objective: Extra-abdominal desmoid tumors are a therapeutic dilemma. Locoregional treatment is often complicated by associated morbidity and high recurrence rates. We aim to assess the outcomes and safety of extra-abdominal desmoid tumors treated with cryoablation.

Methods: An observational cohort study of all patients treated with cryotherapy for desmoid tumors at a single tertiary center was performed. Patients underwent cryotherapy treatment with cryoprobes placed percutaneously within or in close proximity to the target tumor under imaging guidance. The intent of treatment (complete ablation versus partial ablation) was recorded. Treatment outcomes included documentation of symptom improvement in clinical records, as well as change in lesion volume and viable tumor volume. Contrast enhanced cross-sectional imaging was obtained before and after cryoablation. Viable tissue was defined as any enhancing soft tissue. Tumor volume was measured by taking the summation of the areas from regions of interest drawn on every axial slice multiplied by the slice thickness. Safety was assessed by review for treatment related complications both in the short and long term.

Results: We identified 25 patients (age: 12 - 80 years) with 26 discrete extra-abdominal desmoid tumors treated with cryoablation over 44 treatment sessions between 25 February 2010 and 25 February 2020. Cryoablation was performed as first line therapy in 11 patients and as salvage therapy in 14 patients. Previous salvage therapies include surgery (n = 5), radiotherapy (n = 2), tyrosine kinase inhibitor (n = 4), chemotherapy (n = 4), selective estrogen receptor modulator (n=8), non-steroidal anti-inflammatory drug (n = 4), and pegylated interferon (n = 2). All cryoablations were technically successful. The mean imaging follow up was 10.9 months. The mean pre-procedural tumor volume was 236.6 cm^3 (range 2.1 - 949.7). Symptomatic control was achieved in 84.2% of patients. No residual viable tumor was seen on the first imaging follow up in 40% of the patients treated for curative intent. For all patients, at 7 to 12 months, the median change in total lesion volume and viable tumor volume were -6.7% (p=0.809, NS) and -43.7% (p=0.01) respectively. The modified response evaluation criteria in solid tumors (mRECIST) was complete response 0%, partial response 69.2%, stable disease 23.1% and progressive disease 7.7%. 10 patients underwent repeat cryoablation for recurrent disease or as staged procedures. There was 1 major complication (2.4%) consisting of a common peroneal nerve injury.

Conclusion: Cryoablation is effective and safe for treatment for local control of extra-abdominal desmoid tumors.


1000
800
600
400
200
0
Volume (cm³)
TLV
VTV
Pre-ablation
0-6 months
7-12 months
13-24 months
>24 months
Time Following Cryoablation


10 - 12 months mRECIST
100
80
60
40
20
0
-20
-40
-60
-80
-100
Change in tumor from baseline (%)
Partial Ablation
Complete Ablation
PD
PR
Procedures (n = 13)

Poster #036 3445136

DEVELOPMENT OF A NOVEL ORGANS-ON-A-CHIP MODEL THAT ENABLES PREDICTIVE AND CLINICALLY RELEVANT DRUG SCREENING TO DETERMINE EWING SARCOMA ANTI-TUMOR EFFICACY AND CARDIAC SAFETY

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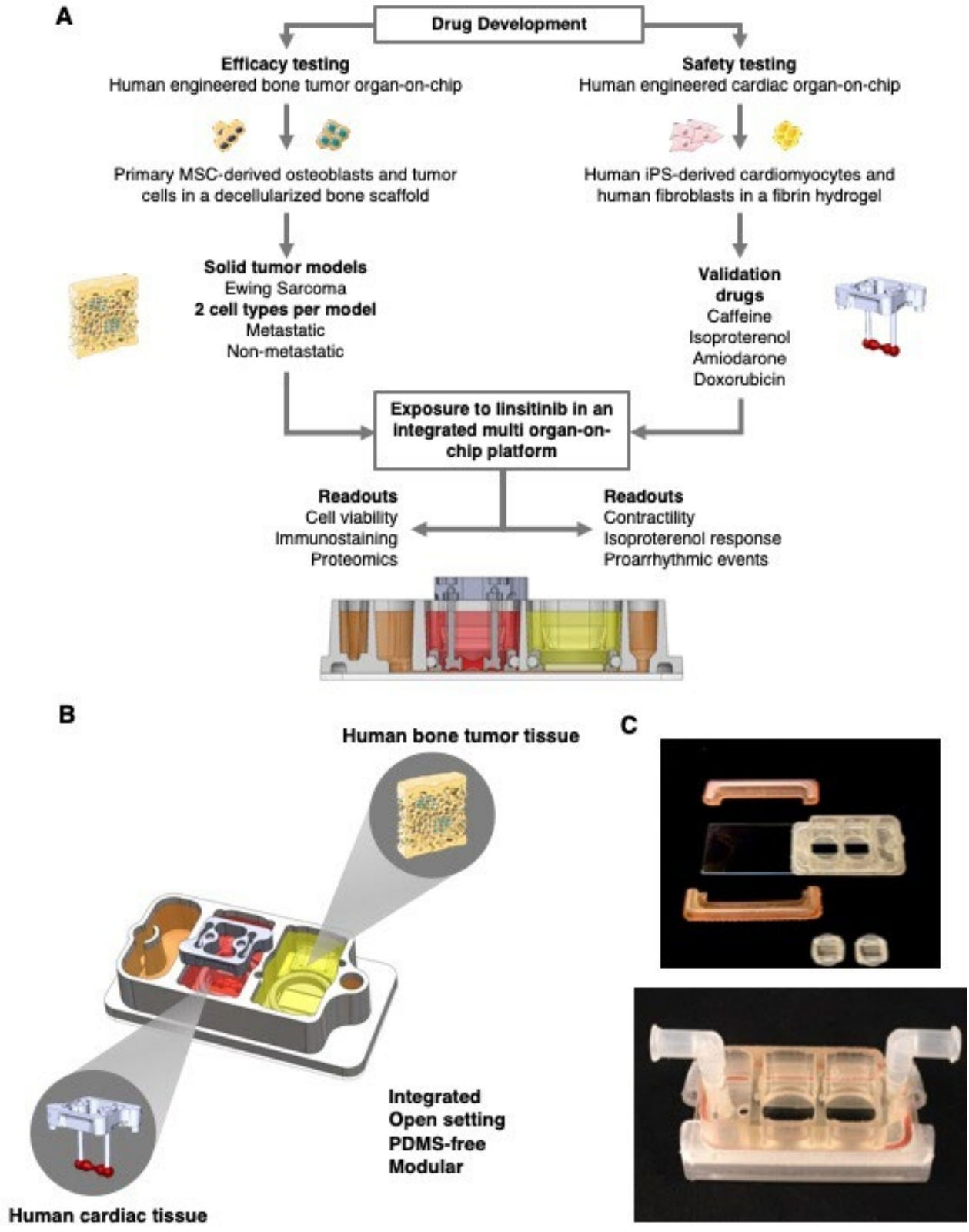
Objective: Traditional *in vitro* drug screening models, like 2D cell cultures, are unable to faithfully recapitulate human physiology in health and disease. As a result, even after years of preclinical testing using established models, new chemo-therapeutic agents often fail during costly clinical trials, largely due to some combination of a lack of efficacy and unwanted non-target tissue toxicity. Organ-on-a-chip (OOC) platforms have since been developed to more accurately mimic native human tissues and therefore improve the preclinical drug development process. Previously, we had published bioengineered models of Ewing sarcoma (ES) and iPSC-derived cardiac tissues: the former recapitulated critical tumor phenotypes within a native bone tissue milieu, while the latter demonstrated adult-like cardiac physiology and function. Both engineered 3D human tissues exhibited a comprehensively higher biological fidelity to corresponding patient tissues than their respective 2D *in vitro* counterparts. Unfortunately, integrated OOC systems have thus far been limited by their complexity, size, and dependence on materials such as polydimethylsiloxane (PDMS) that are highly absorbent for many drugs. In this study, we report the design and utilization of a novel, open setting, PDMS-free, imaging and sampling accessible, polysulfone-based multi-tissue platform uniquely featuring minimal hydrophobic compound binding that allows for integration and co-culture of both our bioengineered ES and cardiac tissues. This enabled us to simultaneously evaluate a drug's anti-tumor efficacy and cardiotoxicity, in this case, linsitinib, an IGF-1R inhibitor being used in a phase II clinical trial.

Methods: The two bioengineered tissues were first treated in isolation and in the novel, integrated OOC platform with linsitinib, an anti-cancer drug recently in phase II clinical trials for ES, according to the 3 week-long clinical regimen, in order to observe which system could better recapitulate the results observed in the trial. A traditional *in vitro* drug study was also carried out using linsitinib on cells grown in monolayer, and results compared against those found with the engineered tissues.

Results: Unlike traditional ES monolayers, our engineered ES tumor tissues had more native-like growth patterns, which actually allowed for a recapitulation of the 3-week long clinical drug regiment. Furthermore, only with our engineered ES tumor tissues were we able to observe distinguished differences in the drug responses of non-metastatic versus metastatic ES, namely that linsitinib is a poor candidate for metastatic ES. More importantly, the responses to drug treatment of the non-metastatic tumor tissues, similar in type to those of the ES patients in the clinical trial, and of the cardiac tissues, when cultured in our novel OOC integrated system, were much more in line with clinical observations than those observed when the tissues were cultured in isolation, which only mimicked the response observed in established, inaccurate, pre-clinical models.

Conclusion: Overall, the integration of both engineered tissue types into our platform improved predictive accuracy for both the direct and off-target effects of linsitinib. Our engineered tumor tissues allowed us to overcome some of the key shortcomings of established Ewing Sarcoma preclinical drug testing models, while our novel platform allowed us to address several of the practical challenges of translating OOC platforms into workable systems for drug screening, with efficient data collection and interpretation. The multi-tissue platform also creates numerous opportunities for future studies due to the ease with which other engineered malignant and healthy tissue models can be incorporated.

Overview of the experimental design and novel multi-tissue platform. A. We developed 2 different organs-on-chips to evaluate anti-cancer drug efficacy (human bone tumor model) and cardiac safety (human cardiac model). Both organs were generated with human cells and characterized and validated before being exposed to linsitinib, a novel anti-cancer therapeutic agent, in isolated static culture and within the novel, perfused multi-tissue platform we developed.
B. Schematic of the 2 engineered human tissues used within the integrated, open, PDMS-free, and modular novel platform.
C. Photographs showing the integrated multi-tissue platform as individual components (top) and in its complete functional state (bottom).



Poster #037 3446023

THE NITRASARC TRIAL- A NON-RANDOMIZED, OPEN-LABEL PHASE II TRIAL EVALUATING EFFICACY AND FEASIBILITY OF COMBINED TREATMENT WITH TRABECTEDIN AND NIVOLUMAB IN PATIENTS WITH METASTATIC OR INOPERABLE SOFT TISSUE SARCOMAS AFTER FAILURE OF AN ANTHRACYCLINE-CONTAINING REGIMEN: INTERIM SAFETY ANALYSIS

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Objective: The NiTraSarc trial evaluates the combination of trabectedin and the anti-PD1 antibody nivolumab in the treatment of patients with metastatic or inoperable soft tissue sarcomas (STS). Here we report data of the safety lead-in, collected from nine patients who had received at least 3 cycles of trabectedin and nivolumab.

Methods: This is a prospective phase II trial (NiTraSarc), consisting of two parallel groups: Group A includes patients with liposarcoma or leiomyosarcoma (abbreviated as L-sarcomas); whereas Group B comprise patients with non-L-sarcomas. Patients in both groups have unresectable or metastatic STS and were pretreated with at least one prior anthracycline-containing regimen. Initially, enrolled patients were treated with three cycles of trabectedin monotherapy, repeated every three weeks (q3w), followed by the combination of trabectedin (1.5 mg/m^2) plus nivolumab (240 mg) starting from cycle 4 (C4) ("late combination cohort") for up to a maximum of 16 cycles. An early stopping rule was set to apply if >3 out of nine treated patients would have an increase in toxicity (compared to trabectedin monotherapy) after administration of three cycles of the combined therapy. In case of a positive result of this safety analysis, treatment schedule was intended to be switched to an "early combination" in which patients receive the combination starting with cycle 2. All patients undergo tumor assessments after cycle 3 and afterwards q9w ± 1 week until disease progression. Primary efficacy endpoint of the trial is progression-free survival (PFS) rate after 6 months (PFS-6) according to RECIST v.1.1. Secondary endpoints are overall response rate, overall survival, PFS and duration of disease stabilization.

Results: Recruitment started in June 2018 and by June 2020, 85 patients have been allocated to the trial (49 in Group A and 36 in Group B). This analysis is based on the first nine patients of the "late combination cohort" who had completed three cycles of trabectedin plus nivolumab. Overall, 20 adverse events (AE grade 3; no grade 4 AEs were observed) have been documented in three out of nine patients. Main grade 3 AEs possibly related to nivolumab were alanine aminotransferase (ALT) increase, gamma-glutamyltransferase (GGT) increase, neutrophil count decrease and white blood cell count (WBC) decrease, 30%, 25%, 15% and 10% of the total number of AEs, respectively. Creatinphosphokinase (CPK) increase, anemia, aspartate aminotransferase (AST) increase and pneumonitis represented 5% of the total number of AEs, respectively. Two AEs (ALT/pneumonitis) occurred in two distinct patients during the safety lead-in phase and were evaluated in detail as potential dose-limiting toxicities (DLTs). Only the ALT elevation >10x Upper Limit Normal (ULN) was an expected side effect of combination therapy, whereas the pneumonitis (SAE due to hospitalization) was resolved after standard corticosteroid therapy and was not considered a DLT according to the trial protocol. Another SAE, a grade 3 neutropenia in one patient was reported to be related to the study drugs but did not meet the criteria for DLT.

Conclusion: Our findings suggest that no changes are required in the risk-benefit considerations or conduct of the NiTraSarc trial following this interim safety evaluation. one DLT occurred in the safety lead-in phase. Thus, the trial continued recruitment without modifications and treatment was switched to combination therapy starting from cycle 2 onward. Due to the timepoint of interim safety evaluation, 28 patients in group A were treated with late combination therapy whereas 27 patients will receive early combination. First safety data of the early combination cohort will be presented at the meeting.

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Poster #038 3446269

TOPP: TENOSYNOVIAL GIANT CELL TUMOR OBSERVATIONAL PLATFORM PROJECT—PATIENT-REPORTED SYMPTOMS AND QUALITY OF LIFE (QOL) FROM A EUROPEAN AND US PROSPECTIVE REGISTRY

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Objective: Diffuse-type tenosynovial giant cell tumor (dt-TGCT) is a rare, locally aggressive, and often recurrent neoplasm of joints and tendon sheaths that can considerably affect patients' quality of life (QoL). Thus far, most reported findings come from small, retrospective case series. The TGCT Observational Platform Project (TOPP) assessed prospectively the impact of TGCT on patient-reported outcomes (PROs).

Methods: TOPP is an observational prospective study conducted in the EU and US that included adult patients with histologically confirmed diagnoses of dt-TGCT seen in sarcoma referral centers between November 2016 and March 2019. Patients were followed for up to 2 years. PRO questionnaires were administered to patients at baseline and at 6, 12, and 24 months follow-up. Demographic, treatments, and PRO at the time of entering the study (baseline) are presented here. Continuous data were reported using either means and standard deviations (SD) or medians and ranges. Pain severity and pain interference scores are graphically visualized by histogram and density kernel.

Results: A total of 181 patients were enrolled (mean age 43.6 years, SD ±14.25), of which 123 (68.0%) had a knee tumor and 112 (61.9%) were female. 137 patients (75.7%) underwent 1 or more surgical treatments prior to baseline, while 53 patients (29.3%) had tyrosine kinase inhibitors (TKIs) prior to entering the study or were still on treatment at baseline (imatinib 26 [14.4%]; pexidartinib 30 [16.6%]). Median reported pain severity score was 3.0 (range 0-8.5), and median reported worst pain score in the last 24 h was 4 (range 0-10), with 10 of 171 patients (5.8%) reporting a pain score ≥ 9. Median score for pain interfering with general activities was 3 (range 0-10), with 10 of 169 patients (5.9%) reporting a score ≥ 9 and median score for pain interfering with enjoyment of life of 2 (range 0-10). Median PROMIS-PF score was 41 (range 23-59), 98 of 160 patients (61.3%) reported limits in doing moderate work, and only 30 of 138 patients (21.7%) used the stairs without difficulty.

Seventy-five/138 patients (54%) were not able to walk at least 15 minutes without any difficulty, and 43/138 (31.2%) could not dress themselves without any difficulty. At baseline, 12 patients (6.6%) had no symptoms. Mean EQ-5D Index and Visual Analogue Scale scores were 0.75 (SD ±0.21) and 69.3 (SD ±20.96), respectively (**Table**). No noteworthy differences on mean EQ-5D Index and Visual Analogue Scale scores were seen with respect to prior surgery or TKI use. Pain Severity Scores by severity (**Figure 1**) and interference (**Figure 2**) kernel estimation are shown.

Conclusion: Most patients with dt-TGCT in the TOPP registry reported moderate pain and varying degrees of limitation in daily activities, with <10% reporting to be symptom-free and 5.8% reporting severe pain. QoL in this dt-TGCT series was low compared to the general population.

Table. Demographics, treatments and patient-reported outcome (PRO) measurements at baseline of TOPP*

Demographics and Treatments	
Age, mean, years (SD)	43.6 (±14.25)
Gender, n (%) Female Male	 112 (61.9) 69 (38.1)
Tumor site, n (%) Knee Hip Ankle Other	 123 (68.0) 13 (7.2) 19 (10.5) 26 (14.3)
Surgery prior to baseline, n (%) Yes No	 137 (75.7) 44 (23.3)
Tyrosine kinase inhibitors, n (%) Yes No	 53 (29.3)† 128 (70.7)
PRO measurements	
Worst stiffness, NRS, mean (SD) (n=168)	4.4 (±2.81)
Worst pain, mean (SD) (N=171)	4.33 (±2.80)
Worst pain, mean (SD) (restricted to patients with "pain other than every-day kinds of pain today", n=92)	5.6 (±2.27)
BPI, pain severity score, median (range) (n=171)	3.0 (0.0-8.5)
BPI, pain interference score, median (n=170)	2.36 (0.0-9.3)
EQ-5D-5L Index, median (range) (n=171)	0.82 (0.16-1.00)
EQ-5D VAS, median (range) (n=172)	70.0 (0.0-100.0)
PROMIS-PF, median (range) (n=166)	40.75 (22.74-58.96)

*Percentages do not take missing data into account
†Some patients received more than 1 systemic therapy prior to baseline

BPI = Brief Pain Inventory; EQ-5D-5L-VAS = EuroQol 5D Visual Analogue Scale; NRS = numeric rating scale; PROMIS-PF = Patient-Reported Outcome Measurement Information System-Physical Function; TOPP = TGCT Observational Platform Project.

Figure 1: Histogram and density kernel of Pain Severity Score at Baseline

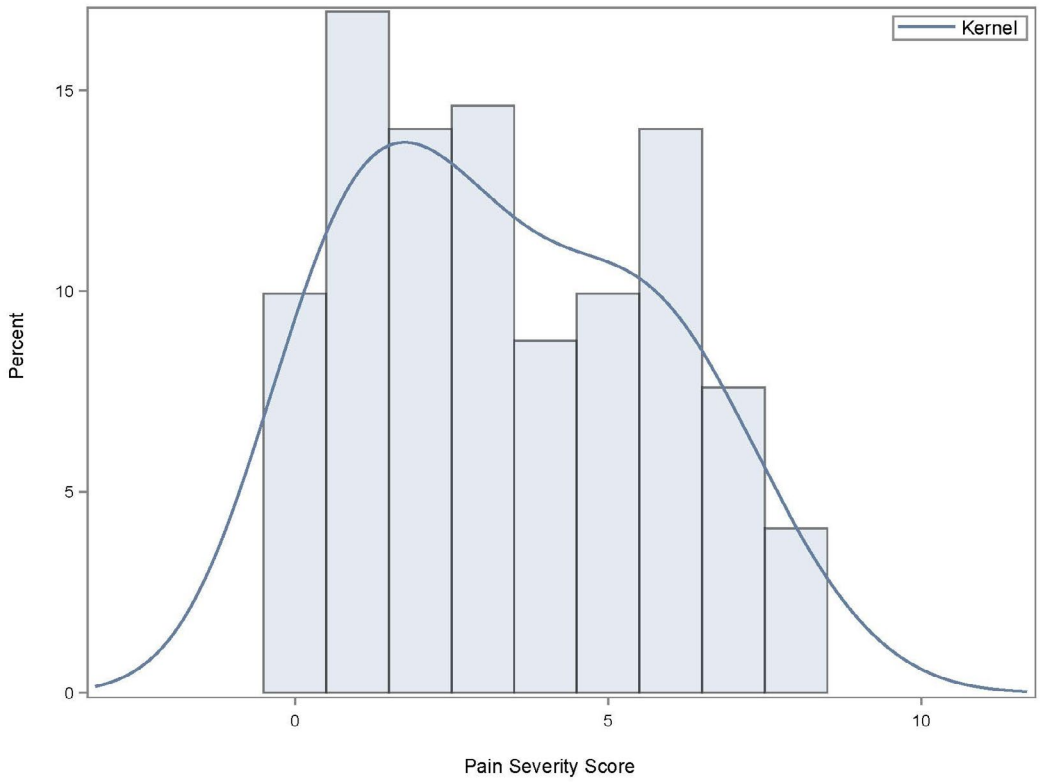
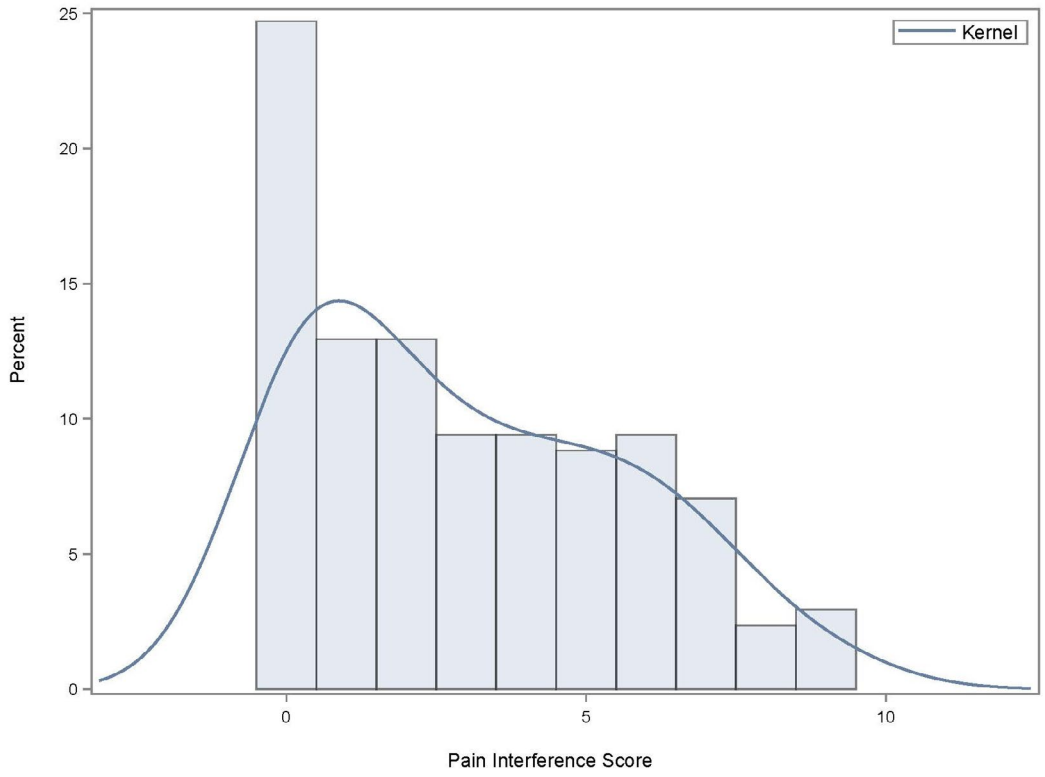


Figure 2: Histogram and density kernel of Pain Interference Score at Baseline



Poster #039 3446499

THE DIFFUSE-TYPE TGCT PATIENT JOURNEY: A PROSPECTIVE MULTICENTER STUDY

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Objective: Diffuse-type Tenosynovial Giant Cell Tumor (dt-TGCT) is a locally aggressive neoplasm located intra- and extra-articular, affecting various joints in the body (mainly the knee), which can have a detrimental effect on quality of life (QoL) in patients who cannot be cured. We present the results of an observational study aimed at describing the TGCT patient journey toward a tertiary sarcoma center, health economics, and disease management.

Methods: The TGCT Observational Platform Project (TOPP) registry was a multinational, multicenter, prospective observational study involving 12 tertiary sarcoma centers in 7 European countries, and 2 US sites. This study enrolled for 2 years all consecutive patients ≥18 years old with a histologically proven diagnosis of primary or recurrent dt-TGCT. Patient demographics and clinical characteristics were collected at study entry (baseline), and every 6 months for 24 months. QoL questionnaires (PROMIS-PF and EQ-5D) were administered at the same time-points. This study presents TGCT-related medical history and healthcare utilization prior to baseline, and current status at baseline. Continuous data were reported using either means and standard deviations (SD) or medians and interquartile ranges (IQR). Categorical variables were summarized as number of observations and percentages of the observations in each category.

Results: Between November 2016 and March 2019, 166 dt-TGCT patients, mean age at diagnosis 39.0 years (SD ±14.42), were included and analyzed. Median time from onset of symptoms until diagnosis was 16.9 months (IQR 4.0–44.0). Seventy-one patients (42.8%) had recurrent dt-TGCT. Prior to TOPP baseline, 139/166 patients (83.7%) received TGCT-related therapy (surgery, radiotherapy, systemic therapy) and 128/166 (77.1%) underwent ≥1 surgical resection(s). Five of 166 (3.9%) received a (tumor) prosthesis. Systemic therapies, mainly tyrosine kinase inhibitors (TKIs) [90.4%] were used in 52/166 patients (31.3%), and median duration of latest systemic therapy prior to baseline was 236.0 days (IQR 118.0–366.0). At baseline, 37 patients were indicated for systemic therapies, of which 21 (56.8%) had severe and 18 (48.6%) had recurrent dt-TGCT. In the 24 months prior to baseline, 76/136 (55.9%) visited a medical specialist ≥5 times and 66/116 (56.9%) missed work for a median of 25.0 days (range 1.0–75.0). Seventeen/146 patients (11.6%) changed employment status (part-time, unemployed, retired), and 26/162 patients (16.0%) required domestic help due to dt-TGCT.

At baseline, 86 patients experienced ≥3 TGCT-related symptoms (i.e., pain, stiffness, swelling, limited range of motion). Mean worst pain and stiffness Numeric Rating Scale scores were 5.6 (SD ±2.29) and 4.3 (SD ±2.83), and 24/166 patients (14.5%) were using analgesics. Clinically impaired median PROMIS-Physical Function (40.75; IQR 36.19–47.01) and EQ-5D-VAS (70; IQR 60–85) scores were observed. Patients under (or awaiting) treatment at baseline had overall worse patient-reported outcomes (PROs) compared to patients allocated with a wait-and-see approach (Table).

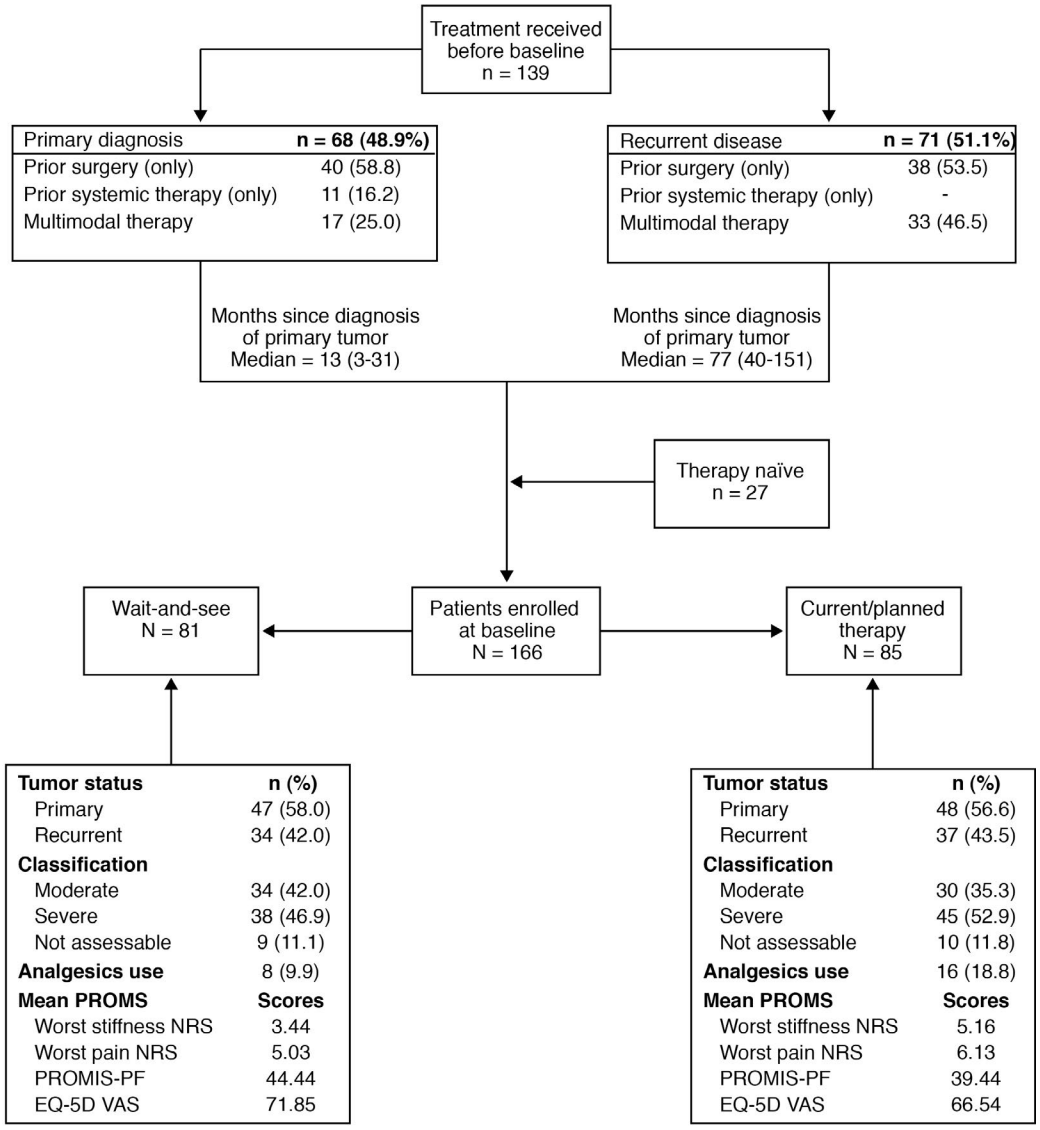
Conclusion: TOPP showed that dt-TGCT affects a relatively young population and can result in serious impairment in daily activities and work life. Diagnostic delay (disease unfamiliarity or misdiagnosis) and frequent recurrences are common and may lead to increased healthcare utilization. Synovectomies are the mainstay of treatment, and TKIs are primarily utilized in severe and refractory cases, while a wait-and-see policy was applied for patients with less symptomatology. Finally, patients with a treatment indication have worse PROs, which suggests that PROs are potential important factors in shared treatment decision making (Figure). Since there is a need for multidisciplinary guidelines, PROs must be included in the development of guidelines of a benign but debilitating disease.

Table. Patient-reported outcomes

	Wait & See (n=81)	Current / planned treatment (n=85)	Total (N=166)
Symptoms at baseline of TOPP, n (%)			
Pain	56 (69.1)	74 (87.1)	130 (78.3)
Stiffness	36 (44.4)	55 (64.7)	91 (54.8)
Swelling	44 (54.3)	58 (68.2)	102 (61.4)
Limited range of motion	39 (48.1)	67 (78.8)	106 (63.9)
≥3 symptoms	31 (38.3)	55 (64.7)	86 (51.8)
Pain as most disturbing symptom	56 (69.1)	43 (52.4)*	99 (60.7)†
Use of analgesics	8 (9.9)	16 (18.8)	24 (14.5)

* Population is n=82.
† The total population for pain as most disturbing symptom is N=163.
TOPP = TGCT Observational Platform Project.

Figure. Flowchart TGCT-related treatments



EQ-5D VAS = EuroQoL 5D Visual Analogue Scale; NRS = numeric rating scale; PROMIS-PF = Patient-reported Outcome Measurement System-Physical Functioning; TGCT = tenosynovial giant cell tumor.

Poster #040 3448478

TREATMENT OUTCOME OF SUPERFICIAL LEIOMYOSARCOMA

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Objective: Non-uterine leiomyosarcomas (LMS) are a common type of extremity soft-tissue sarcoma. Superficial (above the fascia) LMS are classified as dermal (cutaneous) or subcutaneous (below the dermis and above the fascia) and deep (below the fascia). Although previous series of LMS found outcome to be associated with the tumor depth, dermal and subcutaneous tumors are often grouped together as superficial LMS when reporting outcomes. Currently there is limited information on examining only superficial LMS and the outcome of treatment. Therefore, the aim of this study was to examine our institutions superficial LMS when with a focus tumor characteristics which could impact outcome.

Methods: We reviewed 82 patients with a superficial LMS. The mean age and follow-up were 57±15 years. Subcutaneous tumors were separated based on depth was classified as dermal (n= 36, 44%; based in the skin) and subcutaneous (n=46, 56%; below the dermis, above the fascia) on the final resection specimen. Dermal cases were treated with negative margin resection, while subcutaneous tumors were evaluated by a multidisciplinary team, with 26 (57%) patient receiving radiotherapy. All surviving patients had at least 2-years of clinical follow-up; with a mean follow up were 7±5 years.

Results: All patients with dermal LMS has the tumor originate in the dermis, however in 18 (50%) there was focal extension into the subcutaneous fat. Tumors which extended into the subcutaneous tissue were larger (mean 3±2 cm vs. 1±0.7 cm, p=0.004) and more likely to be high grade (n=11, 58% vs. n=1, 6%, p=0.001) compared to dermal LMS without focal extension into the subcutaneous fat. Subcutaneous tumors were more likely (p<0.001) to receive radiotherapy compared to patients with dermal LMS (n=24, 52% vs. n=2, 6%).

At most recent follow-up, 69 (84%) patients were alive without evidence of disease, 2 (2%) were alive with evidence of disease, 7(9%) had died of other causes than their leiomyosarcoma and 4 (5%) had died of disease. The 2-, 5- and 10-year disease specific survival (DSS) of superficial LMS was 100%, 98% and 90%, respectively. When examining the DSS based on depth, there was no difference (p=0.14) in the 10-year DSS between patients with dermal (100%) and subcutaneous (86%) LMS. All patients who died of disease (n=4) had high grade tumors (p=0.11) and all were female (p=0.01). The mean age of these female patients was 48±14 years. In addition patients with larger tumors (≥5 cm) were at increased risk of death due to disease (HR 11.24, p=0.01).

Disease recurrence occurred in 8 (10%) and was defined as isolated metastatic disease (n=6, 7%) and isolated local recurrences (n=2, 2%). The mean time to metastatic disease was 3±2 years, and local recurrence occurred at 5- and 9-years postoperative. All disease recurrence occurred in patients with subcutaneous LMS (17% vs. 0%, p=0.008). The 2-, 5- and 10-year metastatic free survival was 100% for dermal tumors. For subcutaneous tumors it was 93%, 91% and 81%, respectively. No analyzed factor was found to be associated with metastatic disease.

Following surgical resection, the mean MSTS93 score was 96±10%, with a higher mean MSTS93 score in patients with a dermal (99±3%) versus subcutaneous (94±13%) LMS.

Conclusion: Overall the results of this study indicate dermal LMS can be managed with a negative margin surgical resection alone; with little impact on survival. However, subcutaneous LMS has a risk for metastatic disease and local recurrence and as such should be evaluated by a multidisciplinary sarcoma team.

Poster #041 3449895

MOLECULAR ANALYSIS OF ARCHIVAL CLEAR CELL SARCOMA TISSUE SAMPLES FROM EORTC TRIAL 90101 "CREATE" AND CORRELATION WITH RESPONSE TO CRIZOTINIB

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Objective: Approximately 90% of clear cell sarcomas (CCSAs) harbor an Ewing sarcoma breakpoint region 1/activating transcription factor-1 (*EWSR1/ATF1*) rearrangement resulting in aberrant activation of microphthalmia-associated transcription factor (MITF). MITF activates the transcription of multiple genes including *MET*. EORTC 90101 "CREATE", evaluated the MET/ALK/ROS1 inhibitor crizotinib in CCSA and demonstrated that crizotinib provided some clinical benefit for patients with locally advanced or metastatic disease (Schöffski et al. Ann Oncol 2017;28(12):3000). Only sporadic responses were observed. We performed an in-depth molecular analysis of archival tumor material from CCSA patients included in CREATE with the aim to identify genetic alterations that may be relevant for the clinical outcome of CCSA or predictive for response to this agent.

Methods: DNA was isolated from archival primary or metastatic CCSA tissue samples and sequenced using Illumina HiSeq 2500. Low-coverage whole genome sequencing and GISTIC (Genomic Identification of Significant Targets In Cancer) analysis were performed to identify copy number alterations (CNAs). Whole-exome sequencing (WES) was performed to assess the mutational landscape, focusing on mutations affecting Cancer Consensus Genes (CCGs). Kaplan-Meier survival estimates and comparisons with log-rank test were used to assess the correlation between molecular findings and clinical outcome of the patients; the statistical analysis was performed using GraphPad Prism v7, p values <0.05 were considered significant.

Results: In 24 CCSA samples analyzed, the most common whole arm CNAs were gains of 8q (67% of cases), 7q (38%), 7p (33%), 1q (29%), 6p (25%) and 8p (25%); and losses of 9p (54%), 19q (38%), 9q (33%), 17p (33%), 19p (33%), 10p (29%) and 10q (25%). Loss of chromosome 9q was found to be associated with shorter overall survival (p = 0.022). The CNA analysis showed common gains of 8q24.21 (including *EXT1, MYC, RAD21, NDRG1, FAM135B, CSMD3* from the CCG set) and 8q11.23 (*TCEA1*) (in 83% and 67% of cases, respectively). Recurrent losses were observed at 9p21.2 (63%), 9p21.3 (*CDKN2A*, 63%) and 10q26.3 (*MGMT, DUX4*, 54%). We did not find significant correlations between focal CNAs and response to crizotinib.

Using WES, an average of 258 (range 156-473) alterations per sample was found. When considering nonsynonymous mutations in CCG, 211 mutations were identified, affecting 143 genes with an average of 7 (range 7-22) per case. Mutations in 41 CCGs were found in ≥2 samples and the most common mutations detected were *KMT2D* and *SRGAP3* (both in 4/24 cases). The most common alternations were mainly related to DNA repair mechanisms, protein kinases involved in signal transduction, post-transcriptional gene silencing and post-translational modification metabolic pathway. Moreover, the drug gene interaction database (DGIdb v3.0.2) identified 11 potentially actionable targets including *KMT2D*, *TSC2*, *CREBBP*, *DAXX*, *DICER1*, *FBXW7*, *GNA11*, *MAP2K1*, *MAP3K13*, *NOTCH1* and *TBX3*.

Conclusion: We identified a number of molecular alterations in archival CCSAs and provide further insight into the molecular profile of this ultra-rare malignancy, which may potentially lead to the identification of novel targets and treatment approaches.

Poster #042 3450727

OPTICAL SENSOR FOR RAPID BACTERIAL DETECTION AND DIAGNOSIS OF IMPLANT ASSOCIATED INFECTIONS IN CANCER PATIENTS

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Objective: Cancer patients are most vulnerable to opportunistic infections while undergoing systemic chemotherapy. Implant-associated infections (IAI) are devastating complications with incidence rates reaching 40% in cancer patients. The current diagnostic methods available to identify the offending organisms are limited by lengthy lag time-period to process samples, low sensitivities and poor specificity. The lack of prompt and accurate diagnosis of IAI often leads to three main significant clinical concerns: 1) delay of cancer therapy which can lead to poor oncologic outcome, 2) use of broad-spectrum antibiotic therapy that can lead to developing antibiotic resistance, and 3) loss of the implanted medical device leading to loss of function and health care dollars. Therefore, our research team proposes a novel diagnostic technique which relies on developing machine learning algorithms that use "Raman spectroscopy" to detect very low concentrations of bacterial cells and identify the type of bacteria within 15 mins.

Methods: Samples of bacteria are first mixed with a solution of silver nanoparticles that serve to amplify the Raman scattering signal. The sample is then pumped through a microfluidic manifold wherein the cells will enter a hollow optical fiber. Laser light coupled to this fiber excites Raman scattering from the cells flowing through. These scattering events are captured and used for two subsequent tasks. First, the spectrum is classified as either a cellular event or as the spectrum of the background matrix. If the spectrum is classified as a cell, then this event is added to a running count which is used to determine the bacterial concentration. Bacterial spectra are then used to classify the infecting organism. Both of these signal processing tasks are performed by a support vector machine (SVM) machine learning algorithm. To generate known samples for validation of the device, strains of *Staphylococcus aureus*, namely; ATCC 25923, clinical isolates of MRSA (Methicillin Resistance *S. aureus*) and MSSA (Methicillin Sensitive *S. aureus*), were cultured then suspended in FBS to create samples between 0 – 100 CFU/mL. The concentration of these samples was confirmed by conventional culturing and counting.

Results: We are able to discriminate between MRSA and MSSA in FBS with >99% accuracy. Additionally, the ATCC *S. aureus* is predominantly classified as MSSA. We have found a high correlation (R^2=0.9986) between the number of spectral events counted in a 15 mins period and the concentration of the bacteria. The system also presents a low limit of detection of 2.179 CFU/mL (LOD = 3 times deviation of 0 CFU/mL).

Conclusion: In summation, we have been able to employ Raman spectra of cells actively flowing through an optical fiber to both quantify the number of cells in a sample as well as differentiate between clinical isolates of MRSA and MSSA. Furthermore, the fact that the ATCC strain, which is known to be MSSA, is classified as such by the algorithm suggests that there is some preserved structure between susceptible and resistant strains that is apparent in their Raman spectra. This technology represents an exciting path forward for infection diagnosis that is both label and culturing free. The technique we have developed is far faster than conventional methods, which would allow for more timely treatment of IAI and other infections.

Poster #043 3451306

USE OF FDG POSITRON EMISSION TOMOGRAPHY TO PREDICT CHEMOTHERAPY RESPONSE AND OUTCOMES IN PEDIATRIC BONE SARCOMAS

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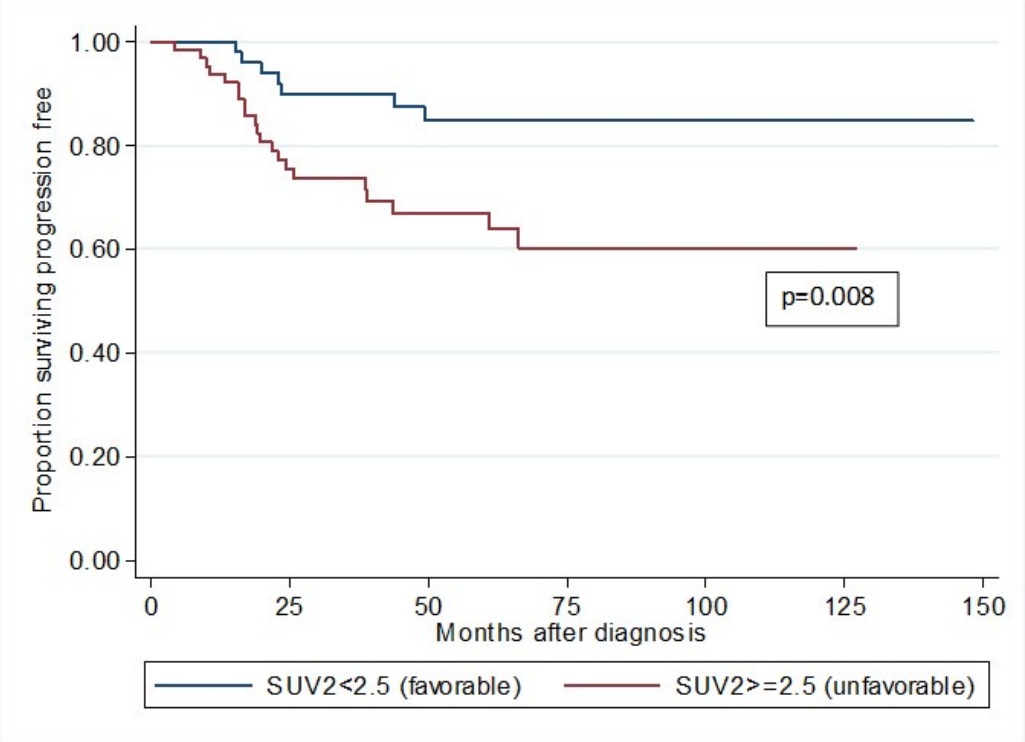
Objective: Osteosarcoma (OS) and Ewing sarcoma (ES) are the two most common pediatric and young adult malignant bone tumors. Response to chemotherapy is a known prognostic factor for both tumor types. Previous small studies have demonstrated the utility of Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) to predict histopathologic response and progression-free survival (PFS). In this study, we describe the relationship between FDG-PET results, chemotherapy response, and clinical outcomes in a larger, more contemporary cohort of pediatric patients with bone sarcomas.

Methods: We performed a retrospective single-institution study of 117 pediatric and young adult patients with OS or ES who underwent FDG-PET imaging both at diagnosis and prior to local control. All patients received neoadjuvant chemotherapy. FDG-PET maximum standard uptake values both before (SUV1) and after (SUV2) chemotherapy were analyzed; additionally, the ratio of SUV2 to SUV1 was calculated. A median of 10.6 weeks (range 8.1-25.6) elapsed between SUV1 and SUV2. Based on previous studies, SUV2 ≥ 2.5 and SUV2:SUV1 ratio > 0.5 were considered poor responses. In patients who received surgical resection (n=99), histopathologic response was assessed using percent tumor necrosis, with unfavorable response defined as <90% necrosis. PFS was defined as time from initial diagnosis to disease progression. Patients who remained progression-free were censored at last follow-up.

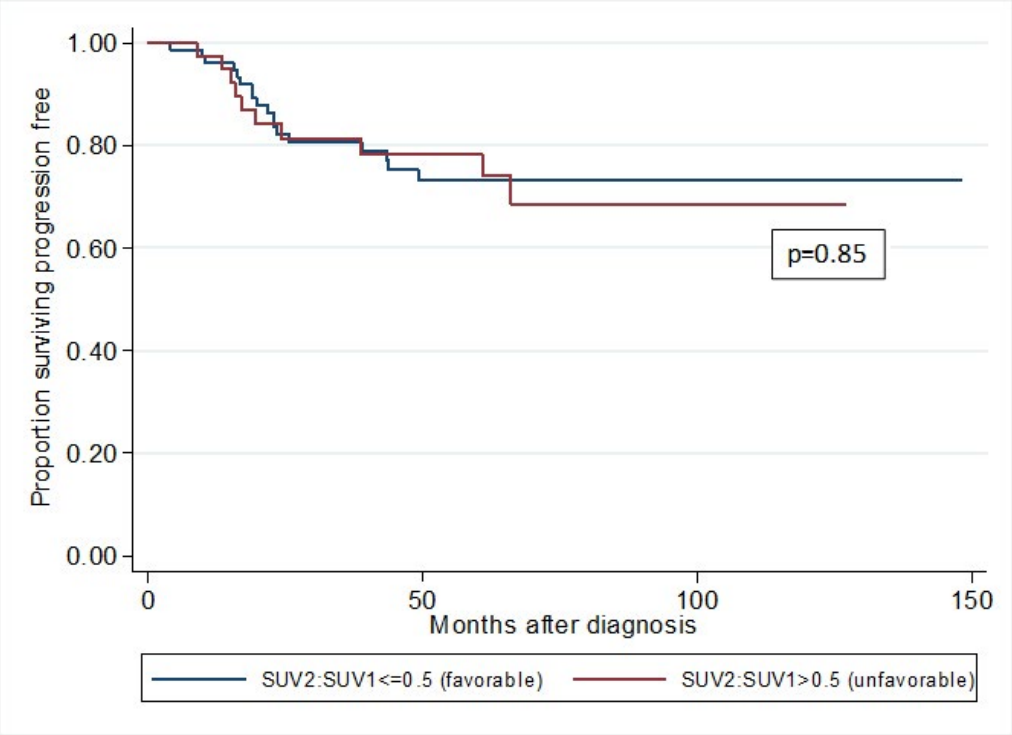
Results: Sixty-one patients with OS and 56 patients with ES were included in this study, with median age of 13.9 years (range 1-27). Median follow-up was 58.1 months (range 6.5-148.1). The majority of patients were male (63.3%). Distant metastatic disease was present in 14 (12.0%) at diagnosis. Overall disease progression rate was 28/117 patients (23.9%); a total of 7 patients (6.0%) died of their disease. Mean SUV1 was 8.4 (range 1.7-34.7) and mean SUV2 was 3.5 (range 1.0-26.3). Mean ratio of SUV2 to SUV1 was 0.47 (range 0.07-2.34). Patients with OS had higher SUV1 and SUV2 values and were more likely to have unfavorable histopathologic responses compared with patients with ES (all $p<0.001$). For patients with OS, those with poor FDG-PET responses (both SUV2 and SUV2:SUV1) were significantly more likely to have unfavorable histopathologic responses (both $p<0.01$). There was no association between SUV2 or SUV2:SUV1 and histopathologic response in patients with ES. SUV2 was associated with outcome (4-year PFS 82.5% for SUV2 < 2.5 (n=53) vs 58.1% for SUV2 ≥ 2.5 (n=64), $p=0.009$ for all patients). SUV2:SUV1 ratio was not predictive of PFS. When patients with OS and ES were analyzed separately, neither SUV2 nor SUV2:SUV1 ratio were predictive of PFS. After adjustment for presence of metastatic disease, SUV2 was associated with PFS (HR 2.80, 95% CI: 1.19-6.62). SUV2:SUV1 was not associated with PFS after adjusting for metastatic disease.

Conclusion: Overall, poor FDG-PET response with SUV2 ≥ 2.5 was associated with unfavorable histopathologic response and inferior PFS, while SUV2:SUV1 ratio > 0.5 was associated only with unfavorable histopathology. However, when analyzed separately by diagnosis, poor FDG-PET response was predictive of poor histopathologic response only in patients with OS and was not predictive of PFS for patients with either OS or ES. These results are similar to previously published data suggesting that FDG-PET results correlate with chemotherapy response but may have limited utility in independently predicting outcomes

Kaplan-Meier estimated progression-free survival by maximum standard uptake value after chemotherapy (SUV2), all patients



Kaplan-Meier estimated progression-free survival by ratio of standard uptake value after chemotherapy to standard uptake value at initial diagnosis (SUV2: SUV1 ratio), all patients



Poster #044 3452161

THE AGE-RELATED IMPACT OF SURVIVING SARCOMA ON HEALTH-RELATED QUALITY OF LIFE: DATA FROM THE DUTCH SURVSARC STUDY

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Objective: Sarcomas are a rare and heterogenous group of tumours which can present at all ages. In sarcoma, aspects of age (e.g. pediatric versus adult) are mainly considered with respect to care and clinical trials, but studies on health-related quality of life (HRQoL) in an adult survivorship population were never analyzed in an age adjusted way. HRQoL is a patient-reported outcome and composes physical, social and psychological aspects of wellbeing and is increasingly considered an important component of patient-centered care. The aim of this population-based study is to compare the HRQoL of sarcoma survivors, stratified by age group, with an age- and sex-matched normative population sample and determine factors associated with low HRQoL.

Methods: This SURVSARC study is a Dutch exploratory population-based cohort study among adult sarcoma survivors based on the Netherlands Cancer Registry (NCR). Survivors diagnosed between 2008 and 2016 were invited to complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). Sarcoma survivors were divided into three groups according to their age at diagnosis; adults and young adolescents (AYA, 18-39 years), older adults (OA, 40-69 years), and elderly (≥70 years). Demographic, tumor and treatment characteristics were obtained from the NCR, which registers treatment from diagnosis until nine months thereafter. HRQoL scores from an age- and sex-matched normative population sample without cancer were compared to the survivors' scores. Logistic regression analyses per age group were conducted to determine the independent association between demographic and tumor characteristics and QLQ-C30 subscales.

Results: In total, 1099 survivors (58% response rate) completed the questionnaire: 186 AYAs, 748 OAs and 165 elderly. Forty-five percent of AYAs, 54% of OAs and 66% of elderly were male ($p<.01$). The median time since diagnosis for all patients was 5.2 years (range. 1.7 – 11.3). The majority of the tumors were localized in the lower extremities, which did not differ significantly between age groups. Bone sarcomas were seen in 41% of AYAs, 22% of OAs and in 16% of elderly survivors ($p<.01$). Of all soft tissue sarcoma diagnoses, AYAs were most often seen with dermatofibrosarcoma protuberans and liposarcoma, whereas elderly were most often seen with myxofibrosarcoma ($p<.01$). AYAs had the highest rate of stage IV disease and elderly stage III disease ($p<.01$). Chemotherapy was more often part of the primary treatment strategy in AYAs than in OAs and elderly survivors ($p<.01$).

In total, 1319 individuals from the normative population were matched with the sarcoma survivors, comparing HRQoL for each age group with their corresponding normative population age group. AYA and OA survivors reported statistically significant and clinically meaningful worse physical, role, cognitive, emotional and social functioning compared to their norm, which was not the case for elderly survivors. On the nine symptom scores, AYAs only reported significantly worse scores on one symptom score (financial difficulties), OAs on seven and elderly survivors did not report worse symptom scores in comparison with their norm.

Extremity localization had an odds ratio of 2.35 (95% CI 1.25 – 4.39) for low physical functioning in AYAs and not in OAs and elderly survivors (Table 1). Chemotherapy as part of the treatment strategy, having a bone sarcoma, and having multiple comorbidities were most often associated with low scores on subscales. A shorter time since diagnosis did not seem to be associated with impaired HRQoL.

Conclusion: In this nationwide sarcoma survivorship study the disease and its treatment had relatively more impact on HRQoL of AYA and OA survivors than of elderly survivors. These results emphasize the need for not only risk adjusted follow-up care related to disease relapse, but also age adjusted care to address the needs that impact important aspects of HRQoL.

Table 1. Age-stratified logistic regression analyses amongst sarcoma survivors for the odds of (1) having a clinically relevant lower score on the concerning subscale compared with the normative population versus (0) having no clinically relevant lower score compared with the normative population.

Adolescents and young adults (n=186)	Low Physical Functioning			Low Emotional Functioning			Low Global QoL		
	OR	95 % CI	p-value	OR	95 % CI	p-value	OR	95 % CI	p-value
Male	0.93	0.50 - 1.73	.82	0.80	0.41 – 1.55	.50	0.90	0.49 – 1.66	.74
Chemotherapy	2.86	1.50 – 5.47	<.01	0.68	0.33 – 1.39	.29	1.49	0.79 – 2.81	.22
Bone Sarcoma	3.09	1.63 – 5.84	<.01	1.32	0.68 – 2.56	.42	1.78	0.96 – 3.30	.07
<5 years since diagnosis	0.96	0.51 – 1.81	.91	1.67	0.85 – 3.26	.13	1.05	0.56 – 1.97	.87
Comorbidities	1.30	0.87 – 1.95	.20	1.49	0.97 – 2.27	.07	2.42	1.53 – 3.82	<.01
Extremities	2.35	1.25 – 4.39	.01	1.05	0.54 – 2.04	.88	1.23	0.67 – 2.27	.50
Older adults (n=748)	Low Physical Functioning			Low Emotional Functioning			Low Global QoL		
Male	0.73	0.54 – 0.99	.04	0.64	0.46 – 0.89	<.01	0.74	0.54 – 1.02	.06
Chemotherapy	2.26	1.50 – 3.39	<.01	1.52	0.99 – 2.33	.06	1.23	0.80 – 1.88	.35
Bone sarcoma	1.11	0.56 – 2.20	.76	0.88	0.41 – 1.91	.75	1.29	0.89 – 1.88	.18
<5 years since diagnosis	1.05	0.78 – 1.41	.77	0.70	0.50 – 0.98	.04	0.78	0.57 – 1.07	.12
Comorbidities	1.67	1.47 – 1.89	<.01	1.44	1.27 – 1.63	<.01	1.68	1.48 – 1.91	<.01
Extremities	1.14	0.85 – 1.53	.39	0.83	0.59 – 1.15	.26	0.70	0.51 – 0.97	.03
Elderly (n=165)	Low Physical Functioning			Low Emotional Functioning			Low Global QoL		
Male	0.74	0.38 – 1.43	.37	0.71	0.34 – 1.50	.37	0.74	0.37 – 1.46	.38
Chemotherapy	1.04	0.25 – 4.32	.96	0.46	0.05 – 3.92	.48	1.04	0.24 – 4.53	.96
Bone sarcoma	3.55	1.40 – 8.97	<.01	0.79	0.29 – 2.12	.64	1.23	0.53 – 2.86	.64
<5 years since diagnosis	0.92	0.48 – 1.75	.79	1.12	0.53 – 2.33	.77	1.65	0.85 – 3.22	.14
Comorbidities	1.41	1.12 – 1.76	<.01	1.36	1.08 – 1.71	<.01	1.35	1.08 – 1.67	<.01
Extremities	1.02	0.55 – 1.92	.94	0.63	0.30 – 1.32	.22	0.85	0.44 – 1.63	.62

Cocks et al. (2011) determined, for each subscale of the EORTC QLQ-C30, the minimal difference in scores between two groups (in this case sarcoma survivors vs normative population) for it to be of small clinical importance. This threshold was used to determine whether individual survivors had a (1) clinically relevant lower score compared with the normative population or if they did (0) not have a clinically relevant lower score compared with the normative population. (Evidence-Based Guidelines for Determination of Sample Size and Interpretation of EORTC QLQ-C30).

Poster #045 3452220

PROMISING ACTIVITY OF AN ENZYME-ACTIVATED DOXORUBICIN PRODRUG IN A PANEL OF PATIENT-DERIVED XENOGRAFT MODELS OF SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcomas (STS) represent a heterogeneous group of rare malignant tumors of mesenchymal origin, comprising more than 70 histological subtypes. Although this group of tumors accounts for only 1% of all adult malignancies, they represent a great clinical challenge because of their poor prognosis, especially in case of unresectable or metastatic disease. The first-line therapy for these patients is doxorubicin, though its response rate is only around 15% and patients are at risk of experiencing severe dose-limiting cardiotoxicity. Consequently, patients with advanced disease are in desperate need of more effective and less toxic treatment options.

We evaluated the efficacy of CBR-049, a tetrapeptidic anthracycline prodrug that is metabolized to doxorubicin by peptidases present in the tumor microenvironment and/or expressed by tumor cells. The efficacy was assessed in 6 patient-derived xenografts (PDX) of leiomyosarcoma (UZLX-STS128 and -STS22), synovial sarcoma (-STS7), intimal sarcoma (-STS185), myxofibrosarcoma (-STS89) and undifferentiated pleomorphic sarcoma (-STS84).

Methods: For every model, NMRI mice (n=30) were transplanted subcutaneously with human tumor tissue from consenting patients on the left flank and randomized in the following treatment groups: control (vehicle), doxorubicin (8.6µmol/kg) and CBR-049 (150µmol/kg). Treatments were administered once weekly by intravenous tail injection for four administrations, followed by two weeks of observation. At the end of experiment (day 36), mice were sacrificed and tumors were collected. Treatment efficacy was assessed by tumor volume evolution, hematoxylin and eosin (H&E) staining and immunohistochemistry for proliferation [phospho-histone H3 (pHH3)] and apoptosis [cleaved poly (ADP-ribose) polymerase (PARP)]. Statistical analysis was performed with Wilcoxon and Mann-Whitney U-test, defining $p<0.05$ as statistically significant.

Results: CBR-049 inhibited tumor growth significantly compared to control in all models tested and showed superior tumor growth inhibition compared to doxorubicin in three doxorubicin responding models (UZLX-STS128, -STS89 and -STS22) and two non-responding models (UZLX-STS185 and -STS84). Histopathological evaluation of tumors confirmed inhibition of proliferation as the mechanism of action in the responding models. CBR-049 achieved significant inhibition of proliferation compared to control in all tested models and superior inhibition compared to doxorubicin in UZLX-STS128, -STS185, -STS22 and –STS84. Moreover, histopathological evaluation revealed complete response with replacement of tumor tissue by scar tissue in UZLX-STS128 and -STS89. CBR-049 was well tolerated, even though 17-fold higher doses were administered as compared with doxorubicin.

Conclusion: In all STS PDX models investigated, CBR-049 revealed superior or at least equal efficacy as compared to doxorubicin without any treatment–related side effects, even though administered doses were 17-fold higher and comparable doses of doxorubicin would be lethal. These results warrant further testing of CBR-049 in the clinical setting.

Poster #046 3452295

BACTERIOPHAGE COCKTAIL TO IMPROVE TREATMENT OF IMPLANT-ASSOCIATED BACTERIAL INFECTIONS IN CANCER PATIENTS

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Objective: Cancer patients are most vulnerable to opportunistic infections while undergoing systemic chemotherapy. Implant-associated infections (IAI) are devastating complications with incidence rate of 50-70% in cancer patients. Unfortunately, treatment failure of IAI can be as high as 40%. A main reason for treatment failure is antibiotic tolerance due to bacterial production of biofilm, which are communities of bacterial cells within a self-produced matrix that allows bacteria to adhere to surfaces and form a resilient barrier against antibiotics. *Staphylococcus aureus* is the most common cause of IAI biofilm-forming infections and represents 30-40% of all isolated cultures. Methods for antimicrobial therapy that focus on disrupting biofilms are needed to overcome antibiotic tolerance while treating IAI. Bacteriophages (phages) are naturally occurring viruses that can destroy biofilm matrix and kill bacteria. This proposal aims to utilize phages and antibiotics to treat *S. aureus* biofilms which affect cancer patients with IAI.

Methods: *S. aureus* BP043 was utilized in this study. This strain is an IAI clinical isolate, methicillin resistant (MRSA) and biofilm-former. Three lytic phages, namely, 44AHJD, Team1 and P68**,** known to infect *S. aureus*, were tested for their efficiency against *S. aureus* BP043. The ability of the phages to eliminate *S. aureus* BP043 planktonic or biofilm cultures was tested either as singular phages or as a cocktail of the three phages. Planktonic cells were adjusted to ~ $1x10^9$ CFU/mL in tryptic soy broth (TSB) and each phage was added alone or as a cocktail at ~ $1x10^9$ PFU/mL with moi of 1 (a multiplicity of infection). Bacterial growth was assessed by measuring optical densities at 24hr and was compared to the control of *S. aureus* BP043 with no phage. BP043 biofilms was grown for 24hr on plasma sprayed titanium (Ti-6Al-4V) alloy disc surfaces. Mature biofilms were then treated with one of the three phages or a cocktail of the 3 phages for 24hr at ~ $1x10^9$ PFU/mL in TSB. Then, biofilms were dislodged, and bacterial survival was assessed by plating on tryptic soy agar plates. Survival in treated biofilms was compared to control biofilm that was exposed only to TSB.

Results: Planktonic cells growth in the presence of phage 44AHJD was reduced significantly (p <0.0001) after 24hr compared to the control. The other two phages did not show a similar pattern when used alone. The reduction in growth was more pronounced when the three phages were combined together (p <0.0001, compared to the control, p=0.011 3, 44AHJD alone versus 3 phages). Exposing BP043 biofilm to the phage cocktail resulted in more than three logs (CFU/mL) reduction in bacterial load residing in the biofilm while no effect was detected when either vancomycin or each phage was used solely.

Conclusion: We have demonstrated that the usage of lytic phage cocktail contributes to better clearance of planktonic cultures of the *S. aureus* MRSA isolate. More importantly, viable bacteria in the biofilms that were grown on plasma sprayed titanium discs were reduced by more than 37% when a phage cocktail was used compared to using a single phage or vancomycin. This work is aimed at gathering preclinical evidence for using phage as a new therapeutic avenue to treat IAI.

Poster #047 3452402

SYSTEMIC INFLAMMATION RESPONSE INDEX (SIRI) AS A PREDICTIVE FACTOR FOR OVERALL SURVIVAL IN ADVANCED SOFT TISSUE SARCOMA TREATED WITH ERIBULIN

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Objective: Eribulin is a tubulin and microtubule-targeting drug that has clinical benefit in overall survival (OS) for patients with advanced soft tissue sarcoma. Although its efficacy has been confirmed in several clinical trials, no clinically useful biomarkers have been identified. We therefore sought to clarify the predictive factor of eribulin treatment, focusing on systemic inflammation and immune response values.

Methods: This study included 33 advanced STS patients treated with eribulin between March 2016 and September 2019. We evaluated the associations of clinical factors influencing the efficacy of eribulin treatment and systemic inflammatory and immune response including the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the lymphocyte-to-monocyte ratio (LMR), the systemic inflammation response index (SIRI), and the prognostic nutrition index (PNI), with progression-free survival (PFS) and OS using Kaplan–Meier curves and log–rank test. NLR, PLR, and LMR were calculated by dividing the number of neutrophils by the number of lymphocytes, the number of platelets by the number of lymphocytes, and the number of lymphocytes by the number of monocytes, respectively. SIRI was defined as (neutrophil × monocyte)/lymphocyte. PNI was calculated as follows, 10 × serum albumin + 0.005 lymphocyte. Median values were used for NLR, PLR, LMR, SIRI, and PNI as the data were not normally distributed.

Results: The median treatment cycle was 3 cycles (range: 1–18 cycles). The median follow-up duration was 7 months (range: 2–27 months). The median PFS for all patients was 135 days (95% Confidence Interval, CI: 57–226 days), and the median OS was 14 months (95% CI: 8–17 months). The cut-off values were defined by median values as 4 for NLR, 210 for PLR, 2.2 for LMR, 1.5 for SIRI, and 44 for PNI. NLR, LMR, PLR, SIRI, and PNI were not associated with PFS. However, compared with patients with SIRI <1.5, those who had SIRI ≥1.5 had a significantly shorter OS［median OS 15 months (95% Confidence Interval, CI 8– not reached) vs. 7 months (95% CI 3–14), P=0.04］.To analyze why eribulin effectively improved OS but not PFS, we evaluated the impact on OS of the new metastases during initial eribulin treatment and PFS during subsequent treatment. Seven patients experienced new metastases during eribulin treatment, but these were not associated with a change in OS (median OS 13 months vs. 14 months, P=0.77). Next, we analyzed PFS of treatment subsequent to eribulin. Twenty patients were administered the next chemotherapeutic treatment after eribulin, whose regimen was as follows: doxorubicin plus ifosfamide (n=1), trabectedin (n=6), and pazopanib (n=13) cases. Patients with SIRI ≥ 1.5 before eribulin treatment tended to have worse PFS compared with patients with SIRI <1.5 (median PFS 92.5 vs. 133 days, P=0.08). Finally, we compared characteristics of patients depending on SIRI value. There was no difference between SIRI ≥1.5 and <1.5 in general conditions, treatment line, duration until eribulin treatment after detection of recurrence or metastases, histological type and subsequent treatment regimens.

Conclusion: High SIRI values may predict poorer overall survival and the efficacy of subsequent drugs after eribulin treatment among patients with advanced soft tissue sarcoma.

Poster #048 3452426

STING ACTIVATION AS AN IMMUNOTHERAPEUTIC STRATEGY FOR SOFT TISSUE SARCOMA

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Objective: Undifferentiated pleomorphic sarcoma (UPS) is one of the most common adult soft tissue sarcomas (STS). UPS has a strong propensity to metastasize and disseminated UPS is rapidly fatal. New therapies are desperately needed for this aggressive disease. Immunotherapies have largely been ineffective against sarcoma. This can be attributed to the immune-suppressive, T-cell poor, tumour immune microenvironment (TIME) common to most STS sub-types. UPS is a heterogenous disease however the majority of UPS have a cold TIME. Dismantling this immune suppressive TIME will be critical to improve immunotherapy efficacies against STS.

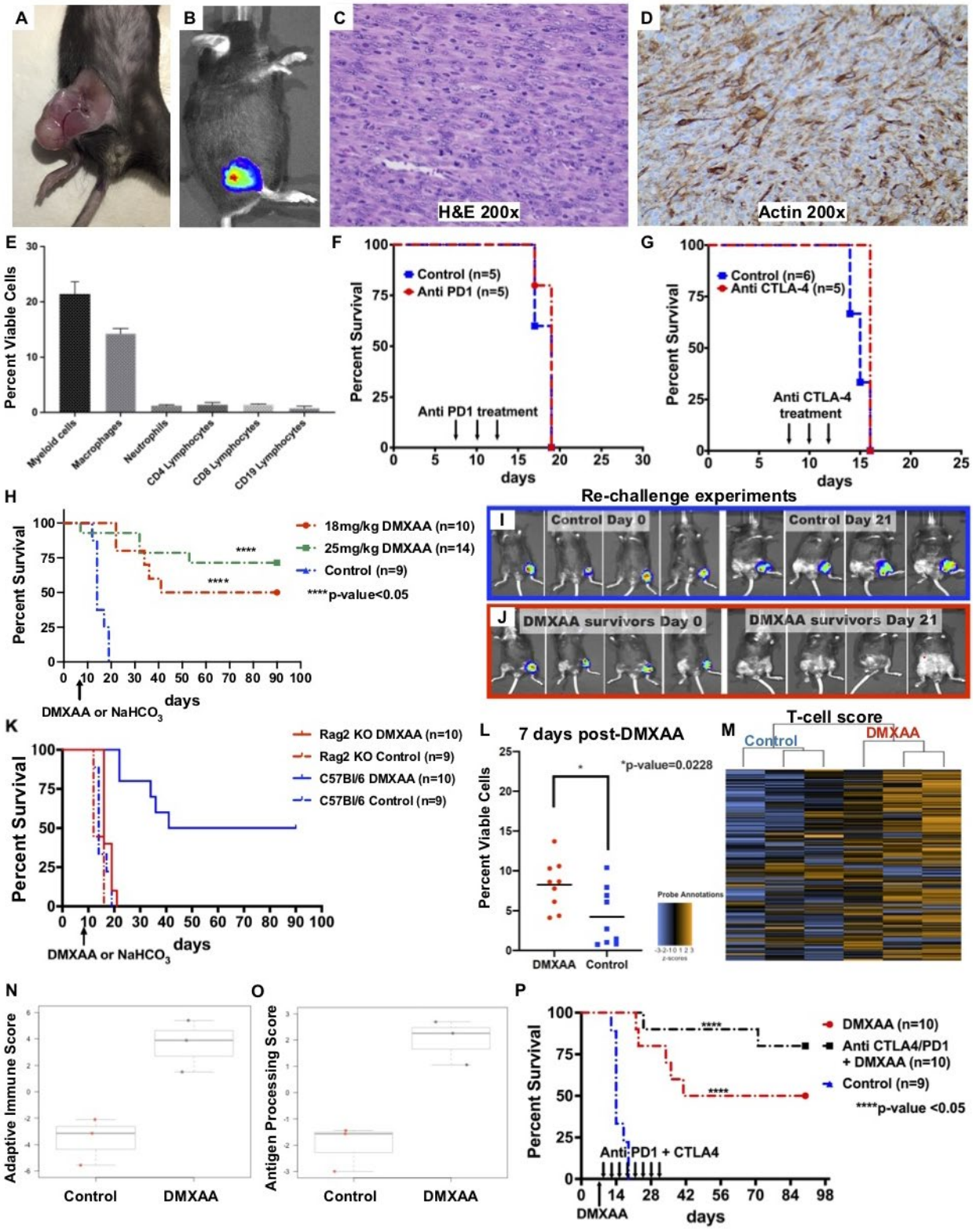
Targeted activation of the STimulator of INterferons Genes (STING) pathway can initiate potent immune-mediated responses against classically "inflamed" solid tumours, however this strategy has not been attempted in immune-suppressive STS models. The purpose of the study was to determine the therapeutic anti-tumour effects of STING activation in a pre-clinical immune suppressive mouse model of UPS.

Methods: UPS tumours are generated via inducible p53 and KRAS mutations in the muscular hindlimb. Low passage UPS cell lines grow rapidly following orthotopic engraftment in syngeneic C57Bl/6 mice and are characterized by a macrophage rich, lymphocyte poor TIME. These UPS tumours are resistant to immune checkpoint blockade. Longitudinal survival following intra-tumoural injection of murine STING agonist, DMXAA was evaluated in UPS-bearing C57Bl/6 and Rag2 knockout (KO) mice. Immune cell phenotypes and transcriptomic immune signatures were quantified following STING therapy. Surviving mice were re-challenged with UPS cells locally or systemically. Tumour progression was assessed through tumour volume measurements and bioluminescence imaging (BLI).

Results: Over 90% of the STING treated UPS-bearing mice survived longer than the vehicle controls. Durable cure was observed in 50-70% of mice. This therapeutic effect was abolished in lymphocyte deficient (Rag2 KO) mice. All surviving mice rejected UPS re-challenge locally and systemically. Flow cytometry and NanoString® Immune Profiling of DMXAA treated tumours demonstrated intra-tumoural recruitment and activation of cytotoxic lymphocytes. Additional therapeutic synergy was observed when intra-tumoural STING therapy was combined with systemic immune checkpoint blockade.

Conclusion: Intra-tumoural STING activation induces potent anti-tumour effects in a pre-clinical mouse model of soft tissue sarcoma. This therapeutic effect is mediated by adaptive immune mechanisms. Further research exploring the role of STING therapy in additional sarcoma models and in synergy with other immune agents, radiation and/or surgery is needed.

Figure 1. Intra-tumoural STING activation induces anti-tumour responses in a murine model of UPS. KRAS and p53 mutations in the mouse tibialis anterior results in isolated hindlimb tumours (A) which are detectable using BLI imaging (B). Resultant tumours show classic UPS characteristics on histology (C), immunohistochemistry (D) and a lymphocyte poor/macrophage rich immune phenotype based on flow cytometry (E). This UPS model is resistant to anti-PD1 (F) and anti-CTLA-4 (G) therapy. Single intra-tumoural injection of DMXAA into UPS bearing mice resulted in complete tumour remission in 50-70% of mice (H). Surviving mice reject local UPS rechallenge (I-J) and the therapeutic effects of DMXAA are lost in Rag2 KO mice (K). CD8+ T-lymphocytes are enriched in DMXAA treated UPS tumours (L), while NanoString® Immune Profiling demonstrates increased T-cell (M), adaptive immune response (N) and antigen processing (O) scores relative to control. DMXAA combined with immune checkpoint blockade (P).



Poster #049 3452445

REGORAFENIB FOR PROGRESSIVE RELAPSED METASTATIC OSTEOSARCOMA IN AN ADOLESCENT

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Objective: While many pediatric cancers have shown great improvement in survival rates over the last 30 years, osteosarcoma (OS) has been lagging behind.The 5-year survival for OS continues to hover around 70% while the rates for metastatic disease are only 10-30% and following Methotrexate, Doxorubicin and Cisplatin (MAP)therapy, patients that relapse, have approximately 15% five-year survival.The NCCN recently updated their guidelines for second line relapsed or metastatic OS to include Regorafenib as a Category 1 recommendation.This came after two phase 2 trials (REGOBONE and SARC024)showed increased progression free survival (PFS) in patients with OS on Regorafenib vs. placebo. Regorafenib is a multikinase inhibitor that targets angiogenic, stromal and oncological receptors involved in tumor growth. Receptor tyrosine kinases (RTK) are enzymes that initiate signaling pathways with the correct ligand interaction. These RTKs are involved in the formation of many cancers, resulting in the pursuit of RTK inhibitor drugs such as Regorafenib.

The REGOBONE trial originally recruited patient with progressive OS >18, however despite opening recruitment to patients >10 years, the youngest patient was 21 years (median 33 years). Utilizing Regorafenib as a single agent showed a median PFS of 16.4 weeks vs. 4.1 weeks in the placebo group with 2/26 patients demonstrating partial response per RECIST criteria. SARC024, another phase II trial utilizing Regorafenib in patients with progressive OS (n= 42, ages 18-76 with a median age of 33) demonstrated improved median PFS of 3.6 months vs. 1.7 months in the placebo group. Even though the encouraging data reported in these studies has been reflected in the NCCN guidelines for second line therapy in OS, the major pediatric oncology groups worldwide have yet to study or endorse Regorafenib for progressive OS. The current report highlights an adolescent with progressive metastatic OS with pulmonary nodules with clinical response after 12 weeks of Regorafenib.

Report the use of Regorafenib for progressive metastatic OS in an adolescent male at a pediatric oncology center.

Methods: A 17 year-old was diagnosed with localized distal femur OS and managed with MAP and en-bloc resection. Following the 29 week regimen he was found to have sub-centimeter lung nodules and was offered surgical resection, but refused.Within 9 months of finishing therapy the patient had massive pulmonary nodules and received Ifosfamide and Etoposide, however after 2 cycles the disease progressed. Third line therapy was initiated with Regorafenib 160mg PO daily for 3 weeks with 1 week off. Cycles repeated every 4 weeks with chest x-rays evaluating response after each cycle.A CT was obtained prior to starting Regorafenib and after 3 cycles of treatment.

Results: At the time of submission the patient was on cycle 4 of Regorafenib. Following cycle 3 a repeat chest CT revealed a decrease in tumor size of 16% per RECIST criteria for the largest 2 lesions.The patient also had no new lesions and multiple others shrunk in size. Patient reported improvement in shortness of breath, chest pain, appetite and fatigue. Cycle 1 of Regorafenib was complicated by diffuse pruritic rash (grade 1) and diarrhea (grade 3). The rash never recurred in subsequent cycles however the diarrhea led to electrolyte disturbance during cycle 2, which prompted a dose reduction to 120mg qday for cycle 3. The patient continues to receive Regorafenib with no new toxicities.

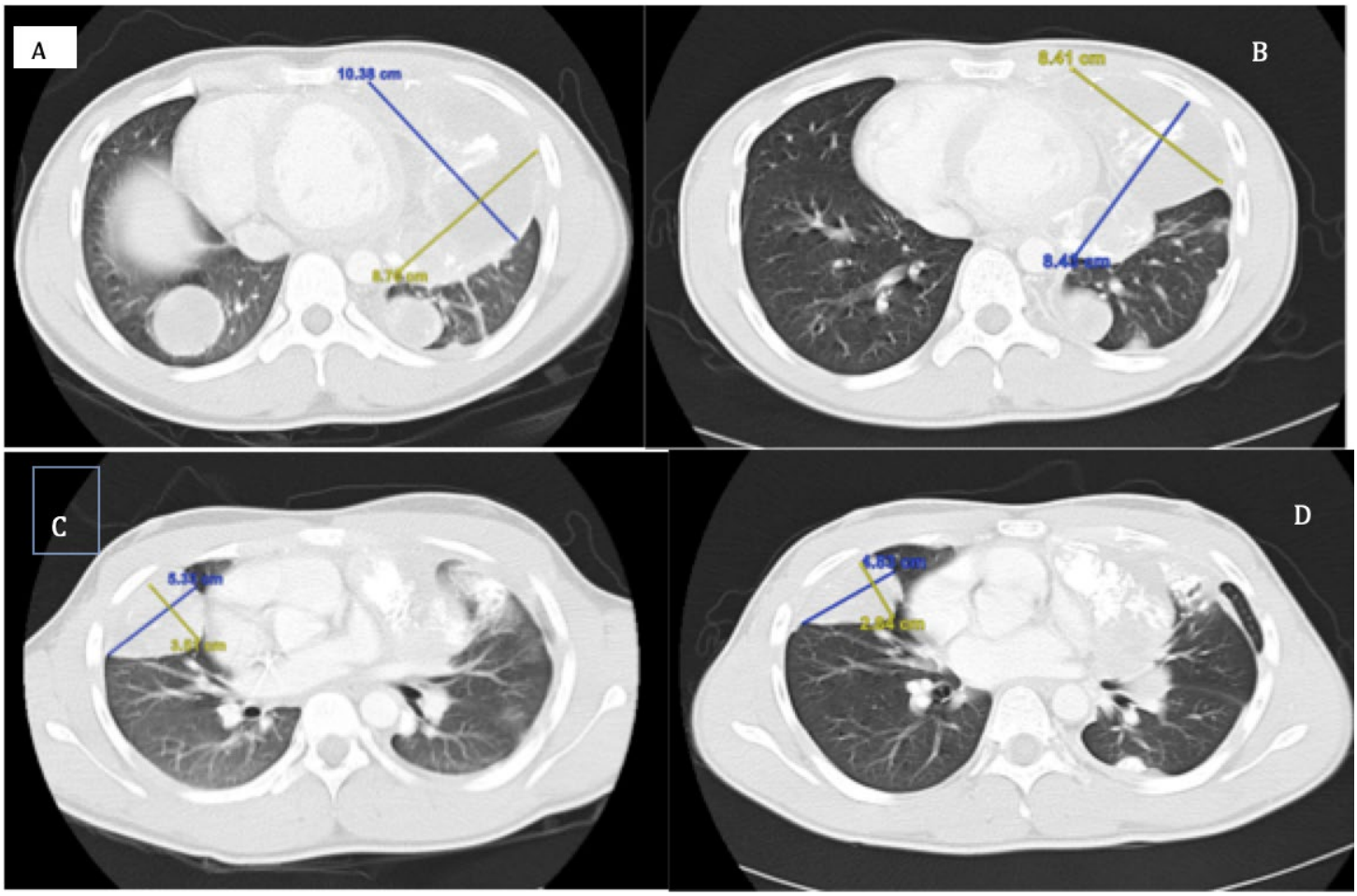
Conclusion: Regorafenib is an oral, potentially safe and efficacious drug for progressive OS. NCCN guidelines support the use of this agent in these patients (Category 1 recommendation). This drug has yet to be incorporated into pediatric clinical trials for progressive OS and has not been reported in other pediatric patients with resistant disease following cytotoxic chemotherapies. Future clinical trials and reports in the medical literature could capitalize on this new agent currently recommended for adult patients with progressive OS.

Figure A: Shows a multiloculated anterior left lung mass prior to starting Regorafenib measuring 10.38cm x 8.70cm

Figure B: Shows the same multiloculated anterior left lung mass after 3 cycles of Regorafenib now measuring 8.41cm x 8.43cm

Figure C: Shows a right middle lobe mass prior to Regorafenib measuring 5.31cm x 4.38cm

Figure D: Shows the same right middle lobe mass after 3 cycles of Regorafenib now measuring 4.83cm x 2.84cm



Poster #050 3452498

OPTIMIZED PATIENT-DERIVED 3D SARCOMA MODEL – ROBUST SYSTEM FOR SARCOMA RESEARCH

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Objective: Recent progress in 3D cell culture models allowed for significant breakthrough in the development of new targeted therapeutics and largely advanced the field of personalized medicine in carcinomas. Unfortunately, the situation is different for the sarcomas: the clinical treatment of sarcoma patients has not significantly changed in the last decade. It is still the combination of surgery, conventional chemo-, and radiation therapy; targeted therapy is very rare, and personalized medicine approach are almost non-existent. Such a discrepancy stems from the high degree of heterogeneity of sarcomas with more that 100 different histopathological subtypes, and the limited knowledge of the molecular drivers of the tumorigenesis and progression.

Our group previously reported the patient-derived 3D (PD3D) sarcoma model, as a tool for a more systematic approach in sarcoma research, however the take in rate for the patient samples was relatively low. Here we report that optimization of our PD3D sarcoma model allowed for a significant improvement of the take-in rate and support the growth of multiple sarcoma subtypes.

Methods: Fresh surgical specimen from incisional biopsy are directly shipped into the lab, allowing for same-day processing. There they undergo several steps of mechanical and chemical dissociation. Subsequently cell aggregates are seeded into 24 well plates in matrix-like scaffolds and allowed to grow until they start forming colonies (Fig 1A-G). After harvesting the cells, they are send for pathology evaluation to confirm origin and diagnosis. Standard-of-care compounds as wells as novel drugs are used for drug sensitivity testing after transferring cells semi-automatically to 384-well plates. Additionally, viability calculation and DigiWest, a multiplex western blot allowing the simultaneous analysis of more than 150 (phospho-) proteins, are performed as reported before.

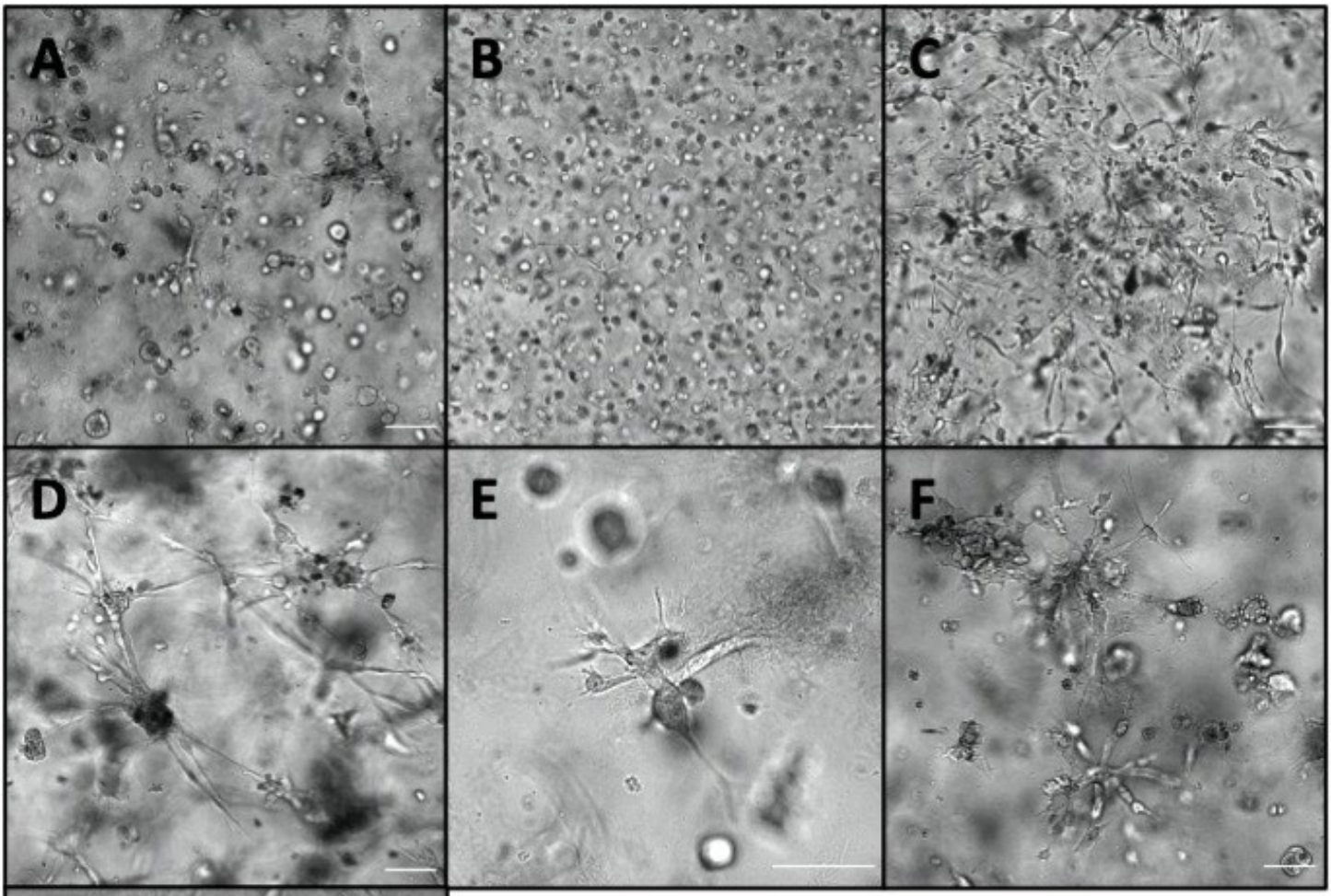
Results: At current stage we obtained 114 patient biopsies. Out of these 46 were reported as sarcoma samples following pathological evaluation. As expected, most common diagnoses within our cohort are Liposarcoma (33%) and Undifferentiated pleomorphic sarcoma (UPS) (28%). Other sarcoma types include: Myxofibrosarcoma (13%), Chondrosarcoma (9%), Leiomyosarcoma (4%), Rhabdomyosarcoma (4%) and Synovial sarcoma (4%). Overall short term take rate is relatively low (39%), as an individual take rate vary strongly within sarcoma subtypes (Fig 1H). However, with the most recent media formulation we were able to maintain short term culture for all of the samples.

Conclusion: Even with the limited number of the samples we were able to accumulate a variety of the different histopathological sarcoma subtypes in our collection. The major technical limitation to the successful establishment of the sarcoma 3D cultures is insufficient amounts of fresh tissue with viable tumor cells. This issue can be overcome by obtaining material through tumor resections, rather than through surgical biopsy.

We hope that further development of our collection will allow us to cover the whole spectrum of sarcomas, generating so much needed tool for investigating soft-tissue tumors, and allowing for successful development of targeted therapeutic approach.

Fig 1. Representative images of sarcoma 3D cultures and general statistics.

A-G – Representative images of different sarcoma subtypes grown in PD3D settings: Liposarcoma (A), UPS (B), Myxofibrosarcoma (C), Chondrosarcoma (D), Leiomyosarcoma (E), Rhabdomyosarcoma (F) and Synovial sarcoma (G), scale bar – 100μm. H – Occurrence of the different sarcoma subtypes within our cohort and associated take in rates.



H

Diagnosis	Occurrance, %	Take in rate, %
Liposarcoma	33	33
UPS	28	38
Myxofibrosarcoma	13	17
Chondrosarcoma	9	75
Leiomyosarcoma	4	50
Rhabdomyosarcoma	4	50
Synovial sarcoma	4	100

Poster #051 3452630

SAFE CLINICAL COMPATIBILITY OF A NON-INVASIVE EXTENDIBLE ELECTROMAGNETIC PROSTHESIS WITH AN IN SITU VENTRICULAR ASSIST DEVICE

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Objective: Osteosarcoma is the most common pediatric primary bone tumor. Standard of care includes a multidisciplinary approach including chemotherapy, wide resection, and limb reconstruction. Combination chemotherapy often includes doxorubicin, an anthracycline, with a rare risk of dose-dependent cardiotoxicity. We report a case of an 8-year-old female diagnosed with osteosarcoma of the distal femur who underwent multidisciplinary treatment including a non-invasive extendible electromagnetic prosthesis for limb length maintenance. She underwent ventricular assist device (VAD) implantation secondary to anthracycline-induced cardiomyopathy and heart failure. We illustrate the safe compatibility between these two devices without adverse effect on VAD function.

Methods: The patient presented with 3 months of right thigh soreness after falling while playing basketball. Plain radiographs demonstrated a heterogeneous lesion in the distal femur metaphysis with cortical destruction and periosteal elevation. On MRI, the tumor was hypointense on T1, hyperintense on T2, and extending beyond the epiphysis with soft tissue extension (Figure 1). Staging showed no evidence of distant or multifocal disease. Hand radiographs demonstrated similar chronologic and bone age. Baseline cardiac echocardiogram and hearing test were normal.

Results: Incisional biopsy confirmed poorly differentiated, high-grade osteosarcoma with myxoid features and 90% p53 positive nuclei that was negative for additional stains or markers. Chemotherapy per European American Osteosarcoma Study-1 (EURAMOS-1) was administered, followed by wide resection and limb reconstruction. Unfortunately, 93 days after chemotherapy, she developed anthracycline-induced cardiomyopathy and rapidly progressed to acute decompensated heart failure (ejection fraction 23%). She was unable to wean from dual inotropes and the HeartWare HVAD was implanted. Compatibility between two commercially VAD devices, the HVAD and the HeartMate 3 (HM3), and the magnetic device used to elongate the prosthesis was assessed prior to lengthening the patient's limb (Figure 2). There were no significant changes in VAD speed, flow, and power when either VAD controller was seven inches from drive unit or within its inner space (Figure 3). With the drive unit at the lowest setting, she was successfully and safely lengthened 3.0mm at 10-months post-operatively with VAD in situ. She remained comfortable and with normal blood pressure during lengthening. She will be listed for cardiac transplant at 12 months from local control surgery if without distant disease or local recurrence.

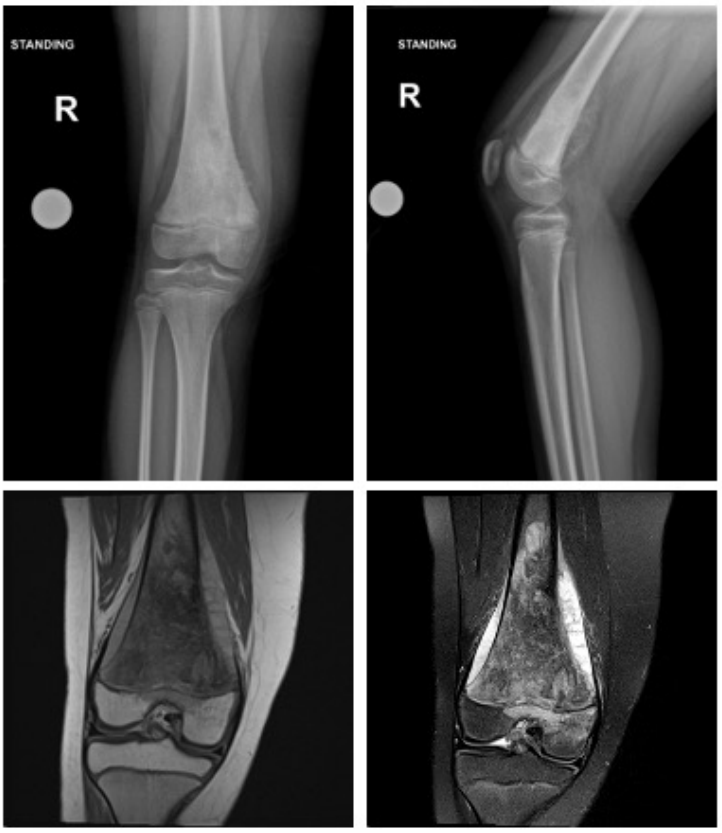
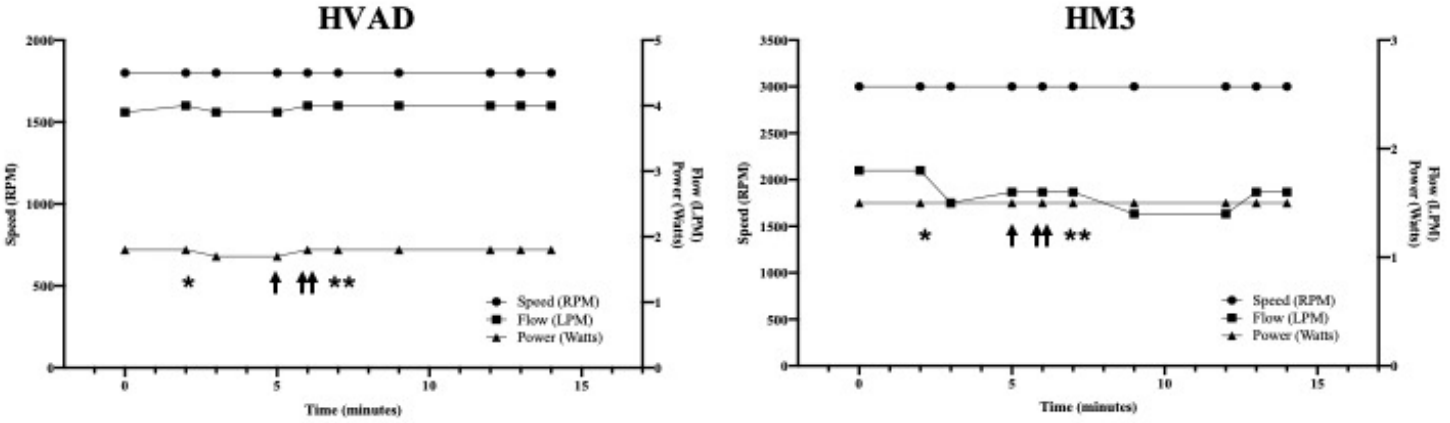


Figure 1

Conclusion: Osteosarcoma is treated with a multidisciplinary approach. Cardiotoxicity and heart failure are rare in anthracycline-treated children, with even fewer children treated with VADs as bridge to cardiac transplantation. We report an extremely unusual situation of a patient treated with an extendible electromagnetic prosthesis safely lengthened with an in situ VAD without adverse effect on VAD function.

Figure 2

Figure 3: Single star- lowest drive unit setting ,100v/70 gauss; single arrow- VAD placed three inches and VAD controller placed seven inches from the drive unit; double arrow- VAD controller placed within the drive unit; double star- highest drive unit setting, 220v/160 gauss (double star).



Poster #052 3452817

SELINEXOR, A FIRST IN CLASS NUCLEAR EXPORT INHIBITOR, FOR THE TREATMENT OF ADVANCED MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

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Objective: Malignant peripheral nerve sheath tumor (MPNST) is rare, representing approximately 5–10% of all soft-tissue sarcomas. They often afflict young to middle-aged adults. This tumor is very aggressive, and surgery remains the only curative treatment for localized tumors. MPNST has a high propensity for distant metastasis following tumor resection. In this setting, standard treatments such as chemotherapy and radiotherapy are often of little benefit, with an average prognosis of less than 12 months. Advances in our understanding of the molecular pathogenesis of these malignancies have revealed multiple signaling pathways and epigenetic regulators, which have been a focus for recent targeted therapy development including inactivation of tumour suppressor pathways. Selinexor (XPOVIO) is a first-in-class oral inhibitor of exportin-1 (XPO1) is approved in refractory multiple myeloma. Selinexor results in nuclear retention and activation of tumor suppressor proteins (TSPs) across several tumor types, including sarcomas. Herein, we report four MPNSTs cases treated with selinexor as single or combination treatment with evidence of partial response or stable disease.

Methods: We performed a retrospective search in the database of Princess Margaret Cancer Centre (Toronto, Canada), University Campus Bio-Medico (Rome, Italy) for patients diagnosed with MPNST who received selinexor (as a mono or combo therapy) between January 2015 and April 2019. All patients who received selinexor within a trial protocol or Single Patient Use Program (SPUP) were eligible to be included. Identified patients were then cross checked with the patient database available at Karyopharm Therapeutics to ensure accurate patient identification. Data collected included patient demographics, disease characteristics, previous line of therapies, selinexor treatment details and clinical outcome.

Results: Between January 2015 and April 2019, four MPNST patients with unresectable or metastatic disease received selinexor. All four patients had their tumor specimens centrally reviewed. Two of these patients received selinexor monotherapy at 60mg orally twice a week, (SPUP and clinical trial NCT01896505) while two others received 80mg once weekly in combination with Doxorubicin at 75mg/m2 (clinical trial NCT03042819). The patient demographics and disease characteristics are summarized in Table 1. Of the four patients, two patients had a partial response (PR) as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, while two others had stable disease (SD). The two patients with PRs were treated with selinexor monotherapy (n=1) as well as in combination with Doxorubicin (n=1). The duration of disease control for the two patients with response was 3 and 3.5 months respectively. A patient with NF-1 associated MPNST had durable stabilization on monotherapy selinexor lasting 13.5 months. In all four patients, the mean duration of disease control was 6 months (range 3 to 13.5 months). Additionally, the target lesion assessments at the time of best response showed a reduction in tumor size in all patients, ranging from -11 to -45%; favorable changes in tumor density were also noted (Table and Figure 1). The treatment with selinexor was associated with a number of well described clinical toxicities such as fatigue, anorexia as well as hematological/biochemical changes, but most are limited to grade 2 toxicities. In one patient, neutropenic fever was observed, but this patient also received concurrent doxorubicin. In 2 of 4 patients, dose reduction occurred due to high or intolerable grade toxicities. A summary of treatment details for selinexor treatment is also summarized in (Table 1).

Conclusion: Advanced MPNST is a rare and highly aggressive sarcoma. It has a high propensity for metastases and resistance to the traditional treatments. Selinexor may be active as a targeted treatment of advanced, metastatic MPNST.

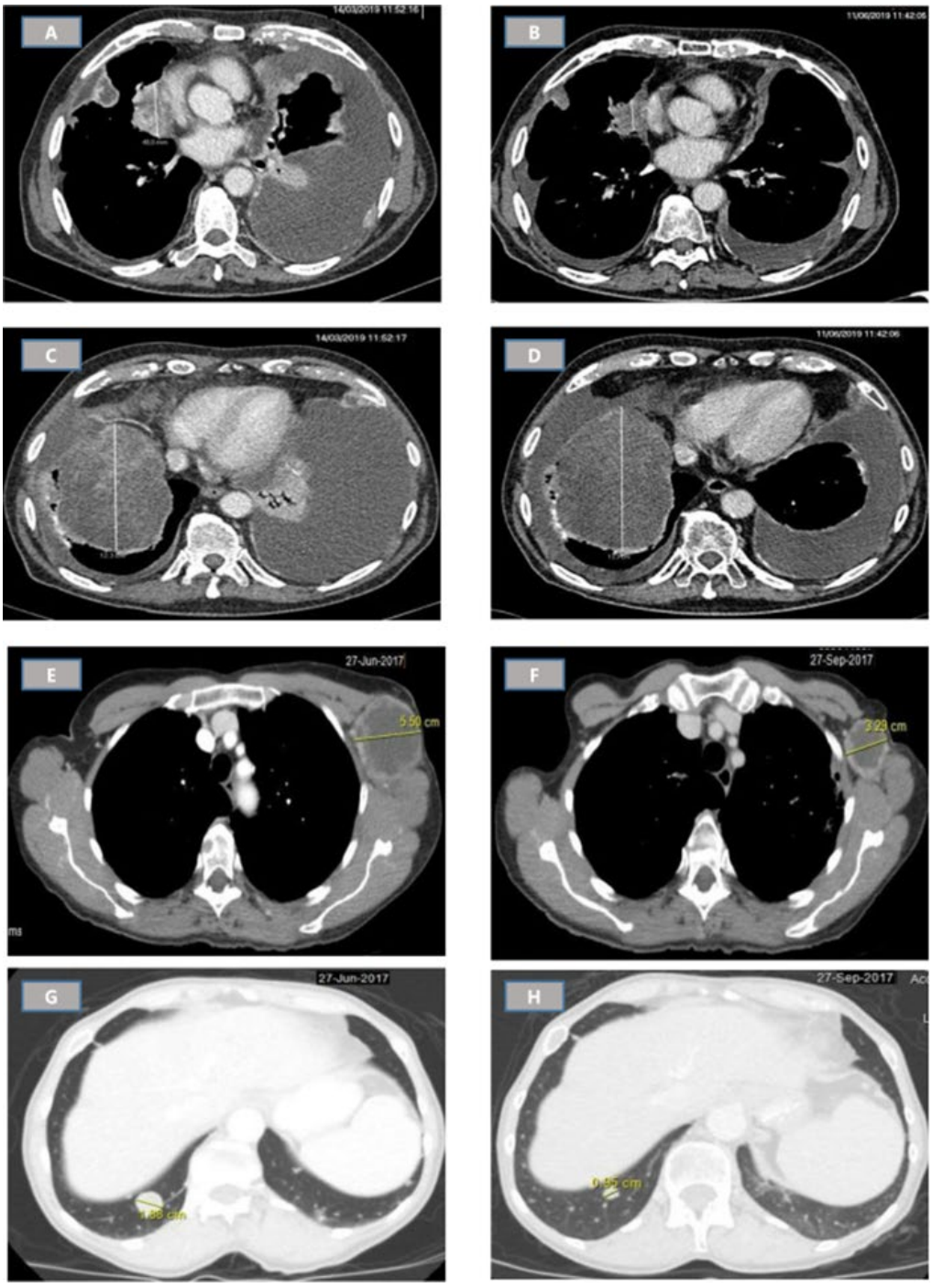
Patient demographics, disease characteristics and treatment summary

Patient characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Treatment Regimen	Selinexor monotherapy	Selinexor with Doxorubicin	Selinexor with Doxorubicin	Selinexor monotherapy
Drug Source	Single Patient Use Program	NCT03042819	NCT03042819	NCT01896505
Gender	Male	Female	Female	Female
Age (y)	79	63	30	65
Ethnicity	Caucasian	Caucasian	Asian	Caucasian
ECOG	1	0	1	1
Relevant History	None	None	Neurofibromatosis (type I)	Neurofibromatosis (type I)
Primary lesion site	Left gluteal	Left axilla	Right gluteal	left iliosacrum
Initial local treatment	Surgery	Radiotherapy (30 Gy/10)	Nil	Surgery
Molecular profile	Focal MDM2 positivity, FISH amplification	BRAF wild type, Unknown MDM2	Negative MDM2	Focal MDM2 positivity
Adjuvant chemotherapy	No	No	No	No
Adjuvant Radiotherapy	No	No	No	Yes (50 Gy/25)
Presentation at advanced disease setting	Multiple metastases	Denovo multiple metastasis	Multifocal local disease	Multiple Metastasis
Site of distant metastases	Lungs and pleura	Lungs, bone, liver	Multiple pelvic masses	Lungs
# of prior therapy to selinexor	2	0	0	1
First line chemotherapy	Doxorubicin/ Olaratumab	NA	NA	ENMD-2076
Second line chemotherapy	Carboplatin - Etoposide	NA	NA	NA
Selinexor treatment details				
Dose	60mg twice weekly	80mg/wk + doxorubicin 75mg/m2	80mg/wk + doxorubicin 75mg/m2	60mg twice weekly
Dose reduction (if any)	40mg twice weekly due to GI toxicities	No dose reduction	60mg/wk; due to neutopenia	No dose reduction
Toxicities (attributable to selinexor)	Nausea, fatigue, loss of appetite, weight change	Anemia, neutropenia, glucose intolerance, hyponatremia, weight loss, nausea	Neutropenia, neutropenic fever, low EF, anorexia, fatigue, anemia,	Nausea, loss of appetite, anemia , fatigue, diarrhea, blurred vision (cataract)
Worst grade of toxicities	G2	G3 (neutropenic fever)	G2	G2
Best response by RECIST 1.1	PR	PR	SD	SD
% of target volume decrease	-40%	-45%	-12%	-11%
Best response by Choi	PR	PR	SD	SD

% Hounsfield Unit change	-50%	-32.7%	-23.6%	-35.7%
Duration of response (months)	3.0	3.5	NA	NA
Time to progression (months)	3.0	3.5	4.2	13.5
Reason of selinexor discontinuation	Compliance	Disease progression	Disease progression	Disease progression

NA, not applicable; G2, grade 2; G3, grade 3; PR, partial response; SD, stable disease.

Figure 1: Representative radiographic images demonstrating response.



(A) Baseline computed tomography (CT) scan of a target lesion in Patient 1; (B) Reduction in tumor size after 3months of selinexor by (40%) according to RECIST 1.1 with an increase in the necrotic component estimated at around 50%; (C) Baseline CT scan of a second target lesion in Patient 1; (D) slight dimensional increase in the target lesion in the order of 1 cm with an increase in the necrotic-colliquative component estimated at around 45% after three months of selinexor.

(E) Baseline CT scan of a first target lesion in Patient 2; (F) Decrease in size of the target lesion 45% according to RECIST 1.1 with an increase in the necrotic component estimated at around 32.7%; (G) Baseline CT scan of a second target lesion in Patient 2; (H) Decrease in size of the target lesion 49% according to RECIST version 1.1.

Poster #053 3452862

UNRAVELLING THE HETEROGENEITY OF SARCOMA PATIENTS' HEALTH-RELATED QUALITY OF LIFE: IMPACT OF PRIMARY SARCOMA LOCATION

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Objective: Sarcoma patients experience many physical and psychological symptoms, adversely affecting their health-related quality of life (HRQoL). HRQoL measurement is challenging due to the diversity of the disease in terms of subtype, location, age of onset, and treatment. Most HRQoL studies focus on patients with extremity sarcoma only while patients with other primary locations are underrepresented. This study aimed to unravel the heterogeneity of sarcoma patients' HRQoL with regard to primary sarcoma location.

Methods: A cross-sectional study (SURVSARC, NTR-7253) was conducted among Dutch sarcoma survivors aged ≥18, diagnosed 2-10 years ago. Primary sarcoma locations were classified as head & neck (HN), thoracic including breast, intra-abdominal including retroperitoneal, pelvic organs including urogenital, axial skeleton (spine and pelvic bones), extremities (upper and lower) and other locations. Sarcoma of the skin was assigned to the aforementioned groups based on anatomical location. Participants completed the EORTC QLQ-C30 as a measure of HRQoL. Sociodemographic and clinical characteristics were collected from the Netherlands Cancer Registry. HRQoL scores were calculated and compared between sarcoma locations. Clinically relevant differences were determined by the EORTC guidelines as large, medium, small or trivial.

Results: 1099 participants were included (response rate 58%) with mean age at diagnosis 54 years (range 18-90). Of all sarcoma locations, patients with sarcoma of the axial skeleton had the lowest mean scores on all functional scales and highest symptom scores of the EORTC QLQ-C30 except for cognitive functioning score (lowest for sarcoma of pelvic organs including urogenital) and for diarrhea and nausea/vomiting scores (highest in intra-abdominal sarcoma). Mean differences were all of clinical relevance, with large or medium differences between the majority of all other sarcoma locations (see Table 1). HN sarcoma patients reported significantly lower cognitive functioning than lower extremity sarcoma patients, with a small clinically relevant difference. Appetite loss, constipation, nausea/vomiting and diarrhoea scores were significantly higher and of small difference for patients with abdominal sarcoma compared to lower extremity sarcoma patients. For the two latter symptoms, scores were also higher and of small difference compared to thoracic and upper extremity sarcoma. Thoracic sarcoma patients reported significantly higher physical functioning than patients with sarcoma of the axial skeleton, lower extremities and other locations, with medium or large differences. Upper extremity sarcoma patients showed significantly higher physical functioning, with small difference, and less pain than patients with lower extremity sarcoma. Results of multivariate analysis will be presented during CTOS 2020.

Conclusion: Different patterns of HRQoL outcomes according to primary tumour location were identified in sarcoma survivors, stressing the need for personalized HRQoL assessment and care. The observed differences could be explained by effects of the primary tumour itself as well as variations in treatment strategies per location, and additional factors, such as age and disease stage. However, the currently used HRQoL measure lacks location-specific problems and is too generic to capture all sarcoma-related issues, emphasizing the necessity for a comprehensive sarcoma-specific HRQoL measurement strategy that covers the heterogeneity of sarcoma.

Table 1: mean score per domain/item for all different locations

	Axial skeleton N=57	Head & Neck N=99	Thoracic including breast N=170	Intraabdominal & retro-peritoneal N=106	Pelvic organs including urogenital N=28	Upper extremities N=138	Lower extremities N=418	Other locations N=83	p-value post hoc ANOVA
EORTC QLQ-C30 domains	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Global health status	67 ± 21	77 ± 20 (a)	80 ± 18 (b)	76 ± 19 (a)	74 ± 22 (a)	80 ± 17 (b)	79 ± 16 (b)	77 ± 18 (a)	<0.001
Physical functioning	65 ± 26	84 ± 22 (a)	88 ± 16 (c)	81 ± 21 (b)	86 ± 18 (b)	87 ± 16 (b)	80 ± 21 (b)	79 ± 24 (a)	<0.001
Role functioning	62 ± 28	79 ± 28 (a)	82 ± 27 (b)	77 ± 26 (a)	88 ± 18 (b)	82 ± 23 (b)	81 ± 26 (a)	73 ± 30 (a)	<0.001
Emotional functioning*	80 ± 23	82 ± 22	85 ± 22	85 ± 19	83 ± 26	89 ± 16	86 ± 18	84 ± 20	0.083
Cognitive functioning	81 ± 21 (d)	81 ± 23 (d)	86 ± 21 (a)	86 ± 20 (a)	79 ± 28	88 ± 17 (a)	89 ± 18 (b)	84 ± 22 (a)	0.002
Social functioning	77 ± 27	84 ± 24 (a)	88 ± 21 (a)	87 ± 20 (a)	83 ± 23 (a)	90 ± 19 (b)	88 ± 20 (a)	83 ± 26 (a)	0.011
Symptom scores									
Fatigue	35 ± 27	24 ± 25 (a)	20 ± 25 (b)	27 ± 25 (a)	26 ± 24 (a)	20 ± 22 (b)	20 ± 21 (b)	29 ± 26 (a)	<0.001
Nausea/ Vomiting	6 ± 13 (d)	3 ± 9 (d)	2 ± 8 (a)	6 ± 16	1 ± 4 (a)	1 ± 7 (a)	2 ± 7 (a)	2 ± 7 (a)	<0.001
Pain	37 ± 33	15 ± 25 (c)	16 ± 24 (c)	16 ± 25 (c)	18 ± 27 (b)	12 ± 20 (c)	17 ± 24 (c)	20 ± 26 (b)	<0.001
Dyspnoea	19 ± 29	13 ± 25 (a)	12 ± 24 (a)	13 ± 23 (a)	14 ± 25 (a)	9 ± 19 (b)	9 ± 19 (b)	10 ± 19 (a)	0.086
Insomnia	35 ± 33	18 ± 26 (b)	18 ± 29 (b)	21 ± 29 (b)	18 ± 31 (b)	16 ± 26 (b)	19 ± 27 (b)	21 ± 28 (b)	0.006
Appetite loss	12 ± 28	8 ± 21 (d)	6 ± 17 (a)	9 ± 22 (d)	5 ± 15 (d)	3 ± 12 (a)	3 ± 12 (a)	5 ± 13 (a)	<0.001
Constipation	15 ± 23	9 ± 24 (a)	7 ± 17 (a)	14 ± 26 (d)	14 ± 25 (d)	7 ± 17 (a)	7 ± 17 (a)	8 ± 20 (a)	0.003
Diarrhea	4 ± 11 (a)	7 ± 15 (d)	3 ± 10 (a)	10 ± 23	10 ± 24 (d)	4 ± 13 (a)	4 ± 14 (a)	7 ± 17 (d)	<0.001
Financial problems	15 ± 26	14 ± 24 (d)	6 ± 18 (a)	8 ± 19 (a)	11 ± 26 (a)	6 ± 18 (a)	9 ± 23 (a)	12 ± 25 (d)	0.02

Range per item is 0-100. Higher scores for a functional scale or global health status/QoL represent higher level of functioning and QoL. Higher scores for a symptom scale or item represent a high level of symptomatology or problems.
a: small difference according to EORTC guidelines, compared to lowest functioning or highest symptom score
b: medium difference according to EORTC guidelines, compared to lowest functioning or highest symptom score
c: large difference according to EORTC guidelines, compared to lowest functioning or highest symptom score
d: trivial difference according to EORTC guidelines, compared to lowest functioning or highest symptom score
*Emotional functioning was not included in the EORTC guidelines

Poster #054 3453418

A RANDOMIZED, OPEN-LABEL PHASE 1/2 STUDY OF RAMUCIRUMAB IN COMBINATION WITH CHEMOTHERAPY IN PEDIATRIC PATIENTS AND YOUNG ADULTS WITH RELAPSED, RECURRENT, OR REFRACTORY DESMOPLASTIC SMALL ROUND CELL TUMOR OR SYNOVIAL SARCOMA

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Objective: Vascular endothelial growth factor (VEGF) and its downstream signals can play a vital role in tumor growth and metastasis. Several soft tissue sarcomas have been shown to express VEGF. When desmoplastic small round cell tumor (DSRCT) and synovial sarcoma (SS) pre-clinical patient-derived xenografts were treated with a mouse-surrogate inhibitor targeting VEGF receptor 2 (VEGFR-2) in combination with standard of care treatments (doxorubicin, cyclophosphamide for DSRCT; doxorubicin, gemcitabine/docetaxel for SS) better tumor efficacy was observed in the VEGFR-2 combinations compared to standard of care alone. Improved treatment options are vital, as DSRCT and relapsed/refractory SS are rare diagnoses with poor prognoses and no defined standard of care treatment. This randomized, controlled study uses multiple innovative design and analytic elements to facilitate rigorous treatment comparisons to address the unique feasibility concerns inherent to investigating novel therapies in rare diseases. This study will evaluate the safety and clinical activity observed in patients with either DSRCT or SS after treatment with the anti-VEGFR-2 antibody ramucirumab in combination with a chemotherapy backbone specific to each indication (cyclophosphamide and vinorelbine or gemcitabine and docetaxel, respectively) compared to chemotherapy alone.

Methods: Children and young adults between the ages of 1–29 years with relapsed, recurrent, or refractory DSRCT or SS not amendable to surgery will be enrolled in a disease-specific, randomized, open-label phase 1/2 trial under the CAMPFIRE master protocol. Approximately 30 patients with measurable disease (Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST]) will be enrolled for each patient population. Patients with inadequate hepatic, hematologic, coagulation, or renal function are not eligible. Eligible patients will be randomized 2:1 to receive either ramucirumab plus chemotherapy or chemotherapy alone, respectively. To ensure the safety of the novel ramucirumab combinations, a safety lead-in period will be observed. Patients with DSCRT will receive cyclophosphamide (25 mg/m^2 per oral once daily) and vinorelbine (25 mg/m^2 intravenous [IV] on days 1, 8, and 15) with or without ramucirumab (12 mg/kg IV on days 1 and 15) on a 28-day cycle. Patients with SS will receive gemcitabine (900 mg/m^2 IV on days 1 and 8) and docetaxel (75 mg/m^2 IV on day 8) with or without ramucirumab (9 mg/kg IV on days 1 and 8) on a 21-day cycle. The primary endpoint of the study is progression free survival, which will be evaluated via a Bayesian analysis incorporating historical control outcomes (derived from real world data), as well as effect-size observed in each patient population. This novel design allows for a reduced proportion of patients to be randomized to the control therapy while maintaining power, in light of sample-size limitations associated with rare diseases. Secondary endpoints include safety and tolerability, as well as overall response rate, duration of response, complete response, characterization of pharmokinetics, and assessment of the immunogenicity of ramucirumab. Key exploratory endpoints include overall survival and the difference in proportion of patients who become eligible for surgical resection of lesions due to documentation of tumor response while on study therapy. This study is open and actively enrolling patients in locations across the United States, Europe, Japan, and Australia. (NCT04145349; NCT04145700).

Results: N/A

Conclusion: N/A

Poster #055 3454087

A RETROSPECTIVE COHORT STUDY ON THE IMPACT OF REGIONAL ANESTHESIA IN SARCOMA RESECTION SURGERY

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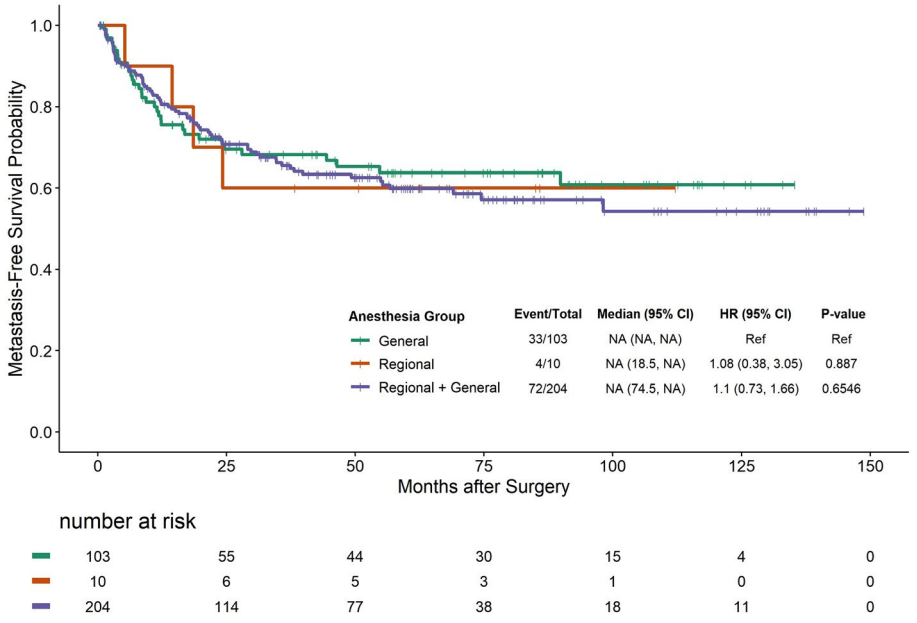
Objective: Previous studies have suggested that the increased rate of metastasis during the perioperative time period may be due to a stress response developed during surgery. Animal models have demonstrated that regional anesthetics (vs. general anesthetics) can diminish the stress response associated with surgery and reduce rates of subsequent metastasis. Despite the basic science research supporting the utility of regional blocks in tumor resection, clinical practice for sarcoma resection remains unchanged. Therefore, the objective of this study is to provide the first robust retrospective cohort study on the impact of regional vs. general anesthesia in sarcoma resection surgery on oncological outcomes.

Methods: This retrospective cohort study reviewed all patients who underwent a surgical resection of a primary bone or soft tissue sarcoma at a single tertiary care referral center from 2007 – 2017. In order to account for variation in surgical techniques, patients were only included if the primary resection surgery was performed by an orthopaedic oncologist. Patients were excluded if they had metastatic disease at the time of surgery or if their sarcoma was located in the trunk or head. The patient cohort was divided into 3 experimental groups based on the type of anesthesia they received during resection: Regional only, General only, and General + Regional. Kaplan Meier survival curves were created to compare overall survival, metastasis, and local recurrence. The date of primary resection was defined as the start time for survival analysis. Hazard ratios (HR) were calculated to compare groups. Results were reported with 95% confidence intervals.

Results: 317 patients were included in this study with a mean follow up time of 51 month after their primary resection. Of the 317 patients, 10 received Regional only, 103 received General only, and 204 received General + Regional anesthesia. Sarcoma subtype and location was not uniformly distributed among anesthesia groups. Compared to patients in the General only anesthesia group, patients in the General + Regional group were more like to have bone sarcoma (38% vs 23 %) and were more likely to have a sarcoma in the distal lower extremity (14% vs 8 %).

The type of anesthesia did not have a statistically significant effect on the probability of local recurrence, metastasis, or death. HR were calculated for General + Regional compared to General only anesthesia groups. The HR for local recurrence was .96 (.48 – 1.93). The HR for metastasis was 1.1 (.73, 1.66). The HR for all cause of mortality was .87 (.59 – 1.28).

Conclusion: There is a growing body of work suggesting the potential benefits of regional anesthetics in the management of cancer. While retrospective studies have shown that regional anesthesia can improve the prognosis in breast cancer, lung cancer and ovarian cancer, no significant improvement has been seen in glioblastoma. Not all malignancies respond to surgery or anesthesia the same way. The results of this study suggests regional anesthetics do not have a protective effect in sarcomas.



Poster #056 3454710

CLINICAL AND MOLECULAR CHARACTERISTICS OF A CASE SERIES OF GIST WITH EXTRA-ABDOMINAL METASTASES

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Objective: Gastrointestinal stromal tumors are rare and can develop anywhere along the gastrointestinal tract. However, the majority of GISTs occur in the stomach and small intestine. Relapse occurs most often in the liver, the mesentery and omentum and development of metastases outside the abdominal cavity are rare. We hereby report on the clinical characteristics and related KIT and/or PDGFRa mutations, or lack thereof, among patients with extra-abdominal GIST metastases.

Methods: The patients were identified through search among the local databases in the Sarcoma Centre of Stockholm and Lund in Sweden, and the medical practice of the authors. Thereafter, a meticulous search in the medical journals of the identified patients was performed for the collection of information regarding the clinical and molecular characteristics of the primary and metastatic lesions.

Results: In total, 15 patients were identified; n=9 (of a total of 457) in Stockholm and n=6 in Lund. The median age at primary GIST diagnosis was 61 years (range 32-74 years). All patients but one were of male gender. Median time from diagnosis to event, defined as development of extra-abdominal metastasis, was 74 months (IQR 20 – 72 months). Localization of primary tumors was as follows: n=7 (47%) in the stomach, n=5 (33 %) in the small intestine, 2 (13%) in the esophagus and 1 (7%) in the rectum. The primary tumors were in general large, mean tumor size 7.6 cm (range 4.2 – 20 cm). Nine patients (60%) had localized disease at the primary diagnosis; six with high-risk GIST, 2 with low risk and 1 did not have available information for classification. About half the patients (n=7) had other synchronous metastases at the time of diagnosis of extra-abdominal metastatic lesions. Four patients developed extra-abdominal metastases during treatment with imatinib, four during other TKIs and seven patients were not receiving any treatment at the time. Localization of extra-abdominal metastatic lesions was: n=4 bone, n=3 lung/pleura, n=3 lymph nodes in the neck, n=2 intramuscular, n=1 brain, n=1 umbilicus, n=1 arm, n=1 scrotum. One patient had synchronous lung and bone metastases. Mutational status for the primary tumor, the metastatic lesion, or both, was available for 11 patients. Of these, six GISTs expressed exon 11 mutations, 1 patient had wild-type GIST at diagnosis but exon 11 mutation at the metastatic site, 1 patient had tumor with exon 9 mutation and 1 patient had tumor with both exon 11 and exon 17 mutations.

Conclusion: Patients diagnosed with extra-abdominal GIST metastases have large tumor at diagnosis. The distribution of primary site appears to follow the general distribution of GISTs. A remarkable difference between this group of patients and the common GISTs are the striking overrepresentation of men. Mutations in exon 11 are the most common in GIST and predispose to imatinib sensitivity. The long interval from diagnosis to development of extra-abdominal metastases could be related to a more indolent biology that, together with sensitivity to imatinib, allows for prolonged survival and subsequent development of atypical metastatic lesions. Whether gender-related factors can influence the risk of extra-abdominal GIST metastases warrants further investigation, although this is hampered due to the rarity of the condition.

Poster #057 3454819

CIRCULATING TUMOUR DNA: A POTENTIAL TOOL FOR SARCOMA MANAGEMENT

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Objective: In recent years, there has been growing interest in the use of circulating tumour DNA (ctDNA) as a biomarker for the monitoring of disease progression in cancer. Referred to as the "liquid biopsy," ctDNA is able to capture the complete genetic landscape of tumours in a non-invasive manner. Due to its ease of collection, samples can be obtained at multiple time points in order to monitor response to treatment and potential recurrence. This is of particular interest in sarcoma, where the ability to better detect recurrence and metastasis can improve prognostic outcomes. The challenge in studying ctDNA lies in the need for extremely sensitive methods of detection, since it makes up only a fraction of the total cell free DNA (cfDNA). However, with advances in droplet digital PCR (ddPCR) it is possible to detect and quantify genetic variants present in extremely low quantities. The objective of this study is to analyze ctDNA isolated from patients with sarcoma to assess its viability as a way to monitor disease.

Methods: Plasma was isolated from 20mL peripheral blood samples collected from 300 pre-operative sarcoma patients, and matched tumour samples from surgical resection were frozen and stored. cfDNA extracted from plasma was quantified using qPCR, and the quality was assessed using capillary electrophoresis. Whole exome sequencing (WES) was performed on matched tumour-blood DNA pairs in order to identify sequence variants in tumour DNA. Primers and probes were then designed to detect those variants as a marker of ctDNA within cfDNA samples. Sensitivity assays were performed using tumour and blood DNA in order to determine the minimum input quantity and percentage of variant DNA required to detect the variant sequence.

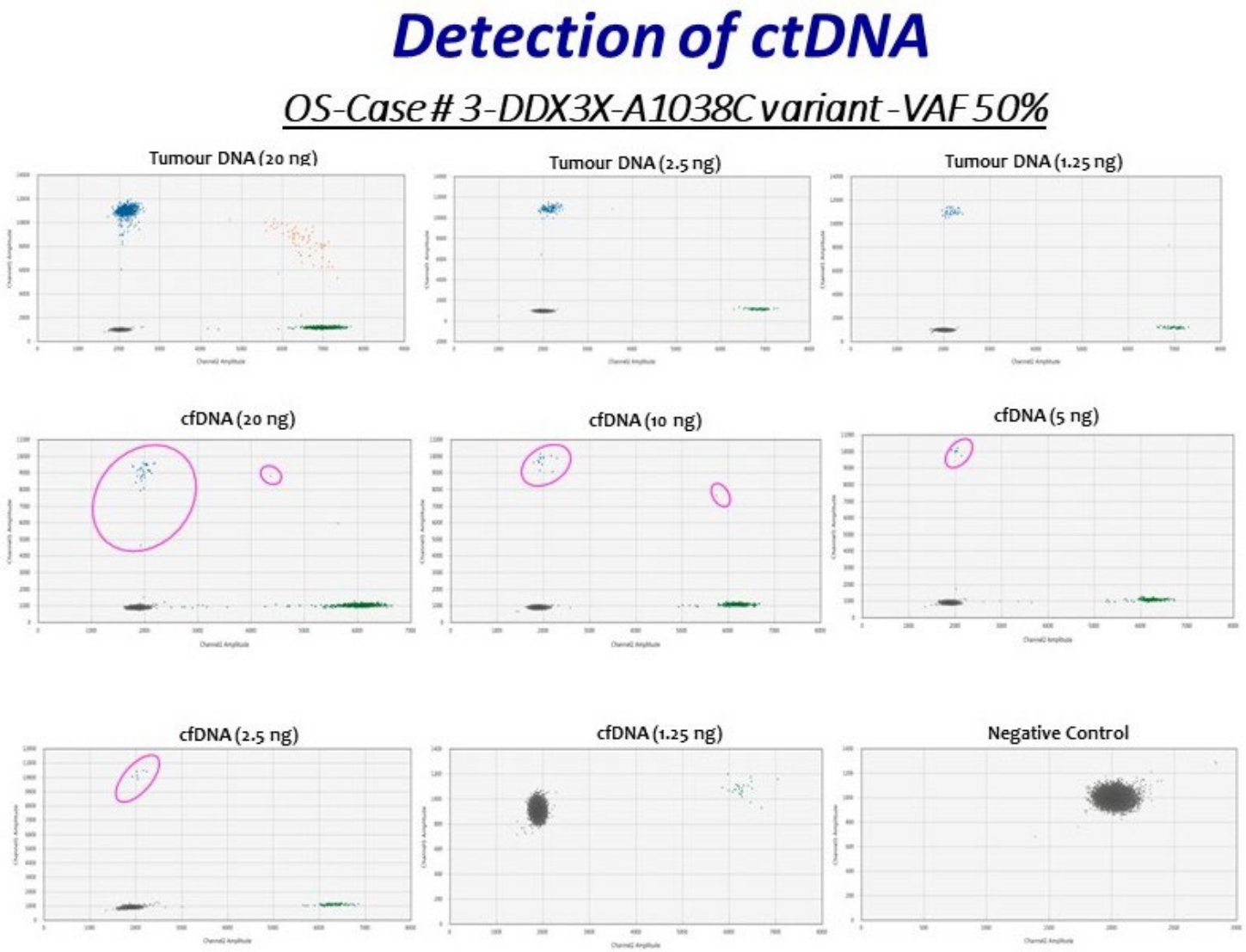
Results: To date, cfDNA has been extracted from 90 cases and quantified by qPCR. Capillary electrophoresis found peaks at approximately 170bp in size, confirming the presence of cfDNA. Whole exome sequencing of six particular cases identified a variety of tumour-specific variations, and variants in SMAD4, COL19A1, DDX3X, ADGRG4, HECW1, and FOXR2 genes were selected as targets to be detected via ddPCR. The variant allele sequence could be detected with as little as 0.25ng of input tumour DNA, with its fractional abundance remaining relatively constant. When diluted with wild-type DNA, the variant sequence was still detectable with as little as 0.5% tumour DNA, depending on the starting fractional abundance of the variant allele. Finally, tumour specific mutations were detected in the cfDNA samples, thus confirming the presence of ctDNA.

Conclusion: This ability to detect ctDNA in the plasma of sarcoma patients is the first step in developing a testing protocol for clinical use. Blood samples from these patients will continue to be collected at follow-up visits, so that plasma may be analyzed for the presence of ctDNA, thus identifying risk of disease recurrence. Additionally, the association between presence of ctDNA and clinical outcome is currently being investigated. Future exploration will include investigating other methods of detection, allowing for multiple mutant targets to be tested for simultaneously.

Identification of tumour specific variants by Whole Exome Sequencing

Case	Gene	Singe Nucleotide Variants	Sarcoma Subtype	Variant Allele Frequency
1	SMAD4	T1584C	Myxofibrosarcoma	86%
2	ADGRG4	T6361C	Liposarcoma	65%
3	DDX3X	A1038C	Osteosarcoma	54%
4	COL19A1	G1252A	Undifferentiated pleomorphic sarcoma	50%
5	HECW1	C1874A	Myxofibrosarcoma	25%
6	FOXR2	C130G	Myxofibrosarcoma	24%

The presence of the tumour specific alteration is visible in the corresponding cfDNA sample in amounts as low as 2.5ng of total cfDNA. Droplet clusters with variant alleles, indicating ctDNA, are circled in pink.



Poster #058 3455149

(GIST) PATIENTS WITH KNOWN MUTATION TRANSITION TO SUBSEQUENT TREATMENTS AT A HIGHER RATE AND HAVE SUPERIOR SURVIVAL COMPARED TO PATIENTS WITHOUT KNOWN MUTATION: RESULTS FROM THE LIFERAFT GROUP (LRG) GIST REGISTRY

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Objective: GIST is the most common sarcoma of the GI tract. Most GIST patients have tumors which are driven by mutations in KIT, PDGFR, RAF, N-TRK, NF-1 or loss of SDH complex. Optimal treatment of GIST patients is determined by selecting a targeted therapy based on knowledge of the driver mutation. However, in the United States less than 30% of patients with metastatic GIST undergo tumor mutation testing. Moreover, patients whose tumors lack mutation testing were found to have inferior survival. We sought to gain insight into the reason(s) mutation testing affects survival.

Methods: This is a retrospective analysis of a long-term observational study of 2076 GIST patients from the LRG GIST registry. Patients were grouped according to their mutational status: those with a known mutation (Known) and those without a known mutation (Unknown). Overall survival (OS) was calculated using the Kaplan-Meier method and the log-rank test. P-values < 0.05 were considered significant. Since mutational testing for GIST mutations did not become clinically available until 2003, patients diagnosed prior to 2004 (n = 631) were excluded from the OS analysis and patients that started 1st line (1L) TKI treatment prior to 2004 (n=536) were excluded from the treatment analyses to reduce survivor's bias. The data cut-off date was 1-13-2020.

Results: Patients diagnosed ≥2004 with a Known mutation (n = 637) have superior OS than patients with an Unknown mutation (n = 811), 14.7 years vs 13.1 years, respectively (p = 0.0002, HR 1.52 95% CI 1.23-1.89). When only patients that began 1L treatment for advanced GIST ≥2004 are considered and OS is calculated from the start of 1L treatment, Figure 1A and Table 1, the median OS of the Known group (n = 429) and Unknown group (n = 329) is 107 months vs 74 months respectively (*p* <0.00001, HR 1.605, 95% CI 1.30–1.98).

Although the median 1L OS was different for the Known and Unknown groups, the median self-reported progression-free survival (srPFS) was extremely similar from 1L through 3L (1L, 28.1 mo. vs. 34.3 mo. (p = 0.3), 2L, 7.0 vs 9.0 mo. (p = 0.3), 3L 6.0 vs 4.3 mo. (*p* = 0.01), Figure 1B, 1C, 1D and Table 1.

Although the srPFS (Figure 1 and Table 1) and Time to Treatment Failure (TTF, Table 1) was very similar (from 1L through 3L), we found a striking difference in the number of treatments that each group had. To understand the impact of access to treatment, we limited further analysis to deceased patients. Patients with Known mutation transitioned to subsequent treatments with a drop-out rate of 15% per line of treatment compared to 47% for the Unknown mutation group. Of deceased patients with a Known mutation starting 1L treatment (n = 241), patients transitioned to the next line as follows (% of pts who received that line of therapy): 2L (85%), 3L (71%), 4L (55%), 5L (41%), 6L (27%) and 7L (15%). For the Unknown group (n = 414), the rate of transition (Figure 2) for patients starting 1L was: 2L (53%), 3L (29%), 4L (15%, 5L (8%), 6L (6%), 7L (3%). This pattern of dropout was similar in different time periods, 2000-2005, 2005-2010 and 2010-2015. The 2015-2020 time period had too few deceased patients for comparison.

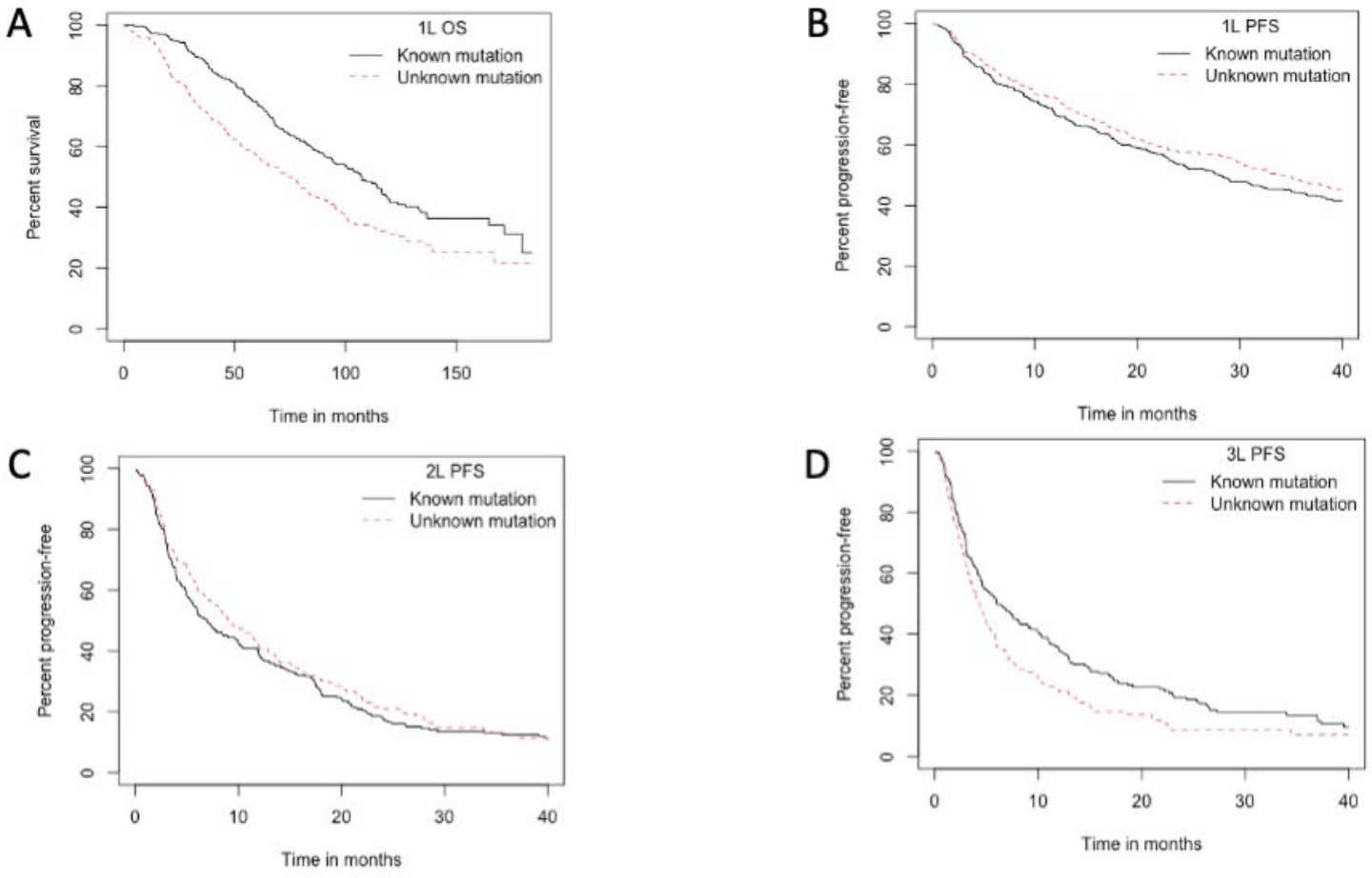
Conclusion: Patients with Known mutation transition to subsequent treatment lines at a much higher rate and have superior survival compared to patients without a known mutation. This may be due to a more proactive healthcare dynamic, such as seeking out treatment from GIST experts, use of off-label treatments and/or clinical trials. Further study including other groups of patients is needed to identify barriers to access treatments. Disparities in access to treatments may be underappreciated and access to treatments beyond approved treatments may improve survival.

Table 1 – Patients with Known mutations have similar treatment response/duration but superior OS

	No. of Pts	OS		srPFS		TTF	
		*Mo.	p value/HR	*Mo.	p value/HR	*Mo.	p value/HR
1L Start ≥2004							
Known	429	107	p < 0.0001 HR 1.61	28.1	p = 0.3 HR 0.90	43.5	p = 0.2 HR 1.12
Unknown	329	74		34.3		36.7	
2L Start ≥2004							
Known	249	40.4	p < 0.0001 HR 1.69	9.0	p = 0.3 HR 1.10	8.4	p = 0.3 HR 0.91
Unknown	344	24.5		7.0		9.9	
3L Start ≥2004							
Known	252	26.2	p = 0.0002 HR 1.56	6.0	p = 0.01 HR 1.34	6.9	p = 0.07 HR 1.34
Unknown	144	16.2		4.3		5.0	

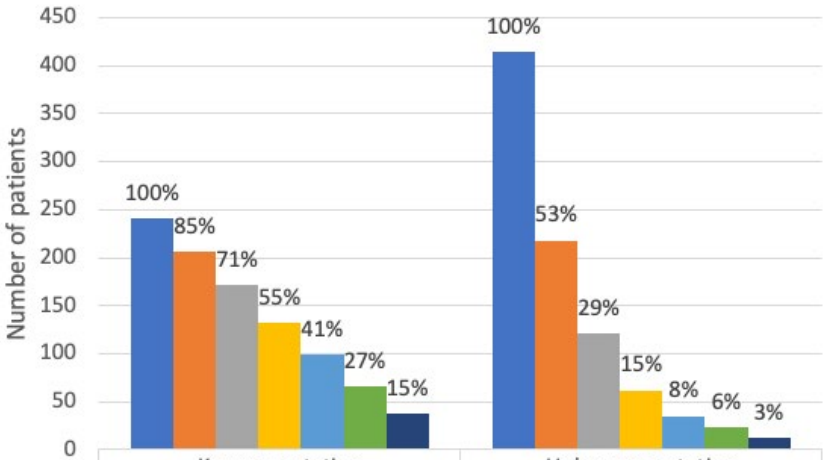
*Median in months

Figure 1 – Treatment efficacy and survival in patients with Known and Unknown mutations



OS was longer for patients with a Known mutation compared to patients with an Unknown mutation (panel A). However, srPFS was similar for these two groups from1L (advanced GIST) through 3L, panels B, C and D. In addition, Time to Treatment Failure (TTF) was also similar from 1L though 3L (see Table 1).

Figure 2 – Patients with Known mutations transition to subsequent treatment lines at a higher rate



	Known mutation	Unknown mutation
1L	241	414
2L	206	218
3L	171	121
4L	132	62
5L	99	35
6L	66	23
7L	37	12

Started 1L treatment 2000-2020

Patients starting 1L treatment are shown in the first column. The percentages shown in the ≥2L columns are the percent of 1L patients that successfully transitioned to that treatment line. For example, in the Known mutation group, 85% of patients that started 1L were able to successfully transition to 2L.

In the Known mutation group, the drop-out rate was 15% per line of treatment compared to 47% in the Unknown mutation group.

Treatments beyond 7L are not shown.

Poster #059 3455363

SUPERFICIAL FIBROMATOSIS LESION SIZE CORRELATES WITH MRI T2 MAPPING AND IMAGE TEXTURE FEATURES

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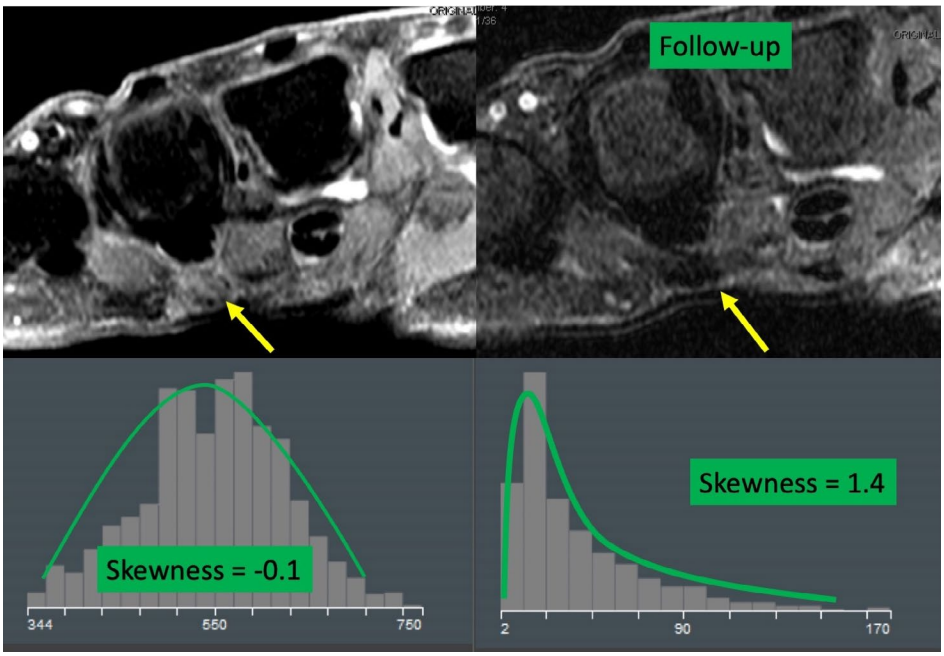
Objective: To determine feasibility of quantifying MRI signal changes over time using image texture analysis and T2 mapping in superficial fibromatoses.

Methods: This IRB-approved retrospective study included 13 patients identified through keyword search of radiology reports for "superficial fibromatosis," "Dupuytren," and "Ledderhose" disease. Single slice regions of interest (ROIs) were drawn in the regionally dominant nodule using Mint Lesion (Mint Medical, Dossenheim, Germany) on conventional proton-density or T2-weighted MRI for radiomics feature analysis, and corresponding T2-maps (TE's: 4.4, 11.9, 19.4, 27.0, and 34.5 ms). Comparisons were made between baseline and follow-up normalized T2 signal ratios and absolute T2 relaxation times, and radiomics features: Shannon's entropy, kurtosis, skewness, mean of positive pixels (MPP), and uniformity of distribution of positive gray-level pixel values (UPP).

Results: There were 19 lesions (11 plantar, 4 palmar; 3 lesions measured pre- and post-treatment). Mean patient age was 60 years, 62% (8/13) were female; mean follow-up was 9.7 months. Lesion long axis at baseline averaged 18.2 mm (std dev 16.2 mm), and decreased almost 10% to 16.6 mm ($p = 0.1$, paired t-test). Normalized T2 signal intensity decreased 23% to 0.55 from 0.71 (std dev 0.33, $p = 0.03$, paired t-test). T2 relaxation time decreased from 46.5 to 39.1ms ($p < 0.001$, paired t-test). Among radiomics features, skewness increased to 0.71 from 0.41 ($p = 0.03$, paired t-test), and entropy decreased from 8.37 to 8.03 ($p = 0.05$, paired t-test); differences in other radiomics features were not significant.

Conclusion: Radiomics analysis and T2 mapping of superficial fibromatosis is feasible; robust decreases in absolute T2 relaxation time, and changes in image textural features such as increased skewness and decreased entropy offer novel imaging biomarkers of lesion collagenization and maturation.



Superficial fibromatosis nodule at the palmar aspect of the ring finger metacarpal head shows heterogeneous T2 signal intensity at baseline; 8 months later follow-up MRI demonstrates homogeneous decreased T2 signal, with increased skewness reflecting change in pixel histogram to predominantly lower values.

Poster #060 3455537

TARGETING THE CMG HELICASE AS A "NEVER" MUTATION TO REDUCE CELLULAR FITNESS IN OSTEOSARCOMA CELLS

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Objective: Osteosarcoma is the most common type of primary bone cancer affecting children and young adults. Despite advances in treatment, 30-50% of patients will have progressive or recurrent disease with a low survival rate. The CMG helicase, the core of DNA replication and cell proliferation, offers a novel therapeutic target in osteosarcoma. Mammalian cells assemble more MCM complexes than will be needed for replication. These function as backups that can be initiated when replication stalls due to cellular stress. Though additional DNA is found in some osteosarcoma cells, the number of MCM complexes appears to be conserved, meaning there are fewer reserve MCM complexes. Additionally, previous studies have shown that reducing the number of MCM complexes sensitizes pancreatic cancer cells to chemotherapy.

Methods: Here, we seek to confirm that the CMG helicase is a suitable target in treating osteosarcoma. Two osteosarcoma cells line were utilized (143B and OS252) and treated with large and small doses of siRNA knockdowns of MCM 4 and MCM7 (subunits of the MCM complex). Once MCM levels were reduced, cells were treated with small doses of chemotherapy drugs (SN-38, doxorubicin, and gemcitabine) for 24 hours. Cells were then assessed for viability and MCM 4 and 7 expression.

Results: We found that 143B contained around 30% more DNA than control cells and OS252 contained 100% more. MCM 4 and 7 expression was conserved among control cells and osteosarcoma cells showing that no additional MCM complexes are created despite the presence of more DNA. MCM 4 and 7 expression is reduced after 48 hours of 3nM siRNA treatment. Additional treatment with chemotherapy drugs reduces cell viability in the treated cells while no effect is seen in cells receiving drug treatment alone. Treatment with high doses of MCM4 and 7 siRNA dramatically reduces cellular fitness in both cell lines.

Conclusion: This study demonstrates that targeting this "never" mutation is a viable therapeutic method for treating osteosarcoma. Additionally, reducing the backup MCM complexes provides an effective sensitizing approach for chemotherapy drugs already utilized in the treatment of osteosarcoma.

Poster #061 3455574

CHARACTERIZING GROWTH UNDER SELECTION FOR OSTEOSARCOMA HETEROGENEITY MODEL

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Objective: Osteosarcoma is the most common bone sarcoma in children, adolescents and young adults. While chemotherapy is universally delivered, benefit from chemotherapy is limited to roughly half of localized patients. Increasingly, intratumoral heterogeneity is being appreciated as a source of resistance to chemotherapy. We wnated to charcterize a model of heterogeneity using co-culture of cell lines.

Methods: In this study we evaluated 6 established osteosarcoma cell lines in terms of genotype (RNAseq, miRNAseq, SNP, copy number) and performed more detailed analyses including proteomics on selected cell lines. All cell lines were evaluated for sensitivity to a panel of 154 unique chemotherapeutic, targeted, and experimental agents at 3 empirically determined concentrations. 2 cell lines with the fastest and slowest doubling times were then were subjected to more extensive analysis in the presence of variable pH and nutritive conditions alone and in co-culture. Finally, therapies were applied towards either changing the final heterogeneity or total cell number.

Results: We present the genotypic and phenotypic characterization of a panel of osteosarcoma cell lines. Two phenotypically divergent cell lines, 143B and SAOS-2, were assayed in co-culture and compared to single culture conditions. We demonstrate that growth kinetics and overall abundance change with perturbations of nutrients, pH, and starting cell concentration. Importantly, the growth characteristics do not change uniformly between these 2 cell lines, allowing for the development of scenarios involving variable growth and treatment conditions that can be gamed and eventually modeled with the goal of fully characterizing this heterogeneous system. Overall, we can affect final heterogeneity of the co-culture with relatively modest environmental perturbations including changes in glutamate and small variations in media acidity. Furthermore, selective inhibitors of one or the other cell line can be used to anticipate final cell line heterogeneity, with the aim of defining optimal treatment regimens that follow First Strike-Second Strike or other evolutionarily guided strategies.

Conclusion: Models of tumor heterogeneity, even a simple two-cell co-culture in vitro, demonstrate that the initial environmental context can impact longer term response and resistance to therapies. These findings advance the notion that cancer therapy may impact subpopulations differently and suggest investigations designed to anticipate changes in tumor heterogeneity in response to therapy. The system can be scaled to allow for greater investigations in terms of combinations and schedules.

Poster #062 3455662

EXPLORATION OF IMAGING BIOMARKERS FOR METABOLICALLY-TARGETED OSTEOSARCOMA THERAPY

Shan Huang[1], *Ling Ren*[1], *Tim Phelps*[4], *Colleen Olkowski*[4], *Anita T. Ton*[4], *Jyoti Roy*[4], *Maggie White*[2], *Aswini Cherukuri*[1], *Stephen Adler*[4], *Karen Wong*[4], *Xiang Zhang*[3], *Falguni Basuli*[3], *Peter Choyke*[4], *Elaine Jagoda*[4], *Amy LeBlanc*[1]
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Objective: Osteosarcoma (OS) is a rare, aggressive cancer of pediatrics/adolescents/young adults for which new therapeutic strategies are needed. We have recently identified a metabolic vulnerability in OS in which glutaminase 1 (GLS1) inhibition, alone and in combination with metformin, yields a therapeutic benefit in OS mouse models. This approach is based on disruption of the bioenergetic demands of tumor progression and metastasis, and shows promise for human translation.

Methods: To complement this therapeutic strategy, three PET clinical imaging agents, [^{18}F]FDG, [^{18}F]FLT and [^{18}F]glutamine were evaluated for their ability to act as companion imaging biomarkers for pharmacodynamic drug response *in vivo*. These PET agents were chosen based upon changes in metabolite profiles from MG63.3 (a human osteosarcoma cell line) xenografts created in SCID mice that received treatment for 7 days with a selective GLS1 inhibitor (CB-839, telaglenastat) and metformin, both alone and in combination. Imaging data were collected before and after therapy, across 4 treatment groups (metformin, telaglenastat, metformin + teleglenastat, vehicle control) and were compared to biodistribution data collected post-treatment.

Results: Alterations in tumor uptake of all 3 PET agents were observed after drug treatment. ^{18}F-FDG uptake was not robust in this tumor model, with SUVmean ranging between 0.7-0.8 at both pre- and post-treatment timepoints. The relative ^{18}F-FDG tumor uptake when compared to muscle increased significantly after treatment with metformin alone, but tended to decrease within all other groups. [^{18}F]FLT uptake increased after therapy across all treatment groups compared to control. [^{18}F]glutamine uptake in the tumor and most other tissues increased with telaglenastat and combination treatment compared to control, which is reflective of the global increase in the available glutamine pool size that occurs with GLS1 inhibition.

Conclusion: Changes in [^{18}F]FDG tumor uptake were informative for measuring a treatment response for metformin as a single agent, but do not provide an evaluation of the impact of glutaminase inhibition alone or in combination with metformin. The increases in [^{18}F]FLT uptake observed are likely due to a compensatory cellular shift toward the thymidine salvage pathway in order to maintain nucleotide biosynthesis in the face of nutrient deprivation. Expected increases in [^{18}F]glutamine uptake that occurred with glutaminase inhibition were not specific to tumor tissue, thus additional pharmacokinetic and multi-timepoint kinetic imaging studies would be required to fully determine the utility of [^{18}F]glutamine imaging in tumor-bearing patients undergoing telaglenastat therapy.

Poster #063 3456222

FACTORS AFFECTING GENETIC CONSULTATION IN ADOLESCENT AND YOUNG ADULT PATIENTS WITH SARCOMA

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Objective: Given a link between sarcomas and Li-Fraumeni syndrome, consideration for genetic counseling is recommended for all adolescent and young adult (AYA) patients diagnosed with sarcoma. The ability of providers to discern genetic predisposition is critical as it facilitates genetic counseling and testing with subsequent screening for patients with heritable cancer predisposition syndromes. Considering the importance of genetic counseling in these patients, we sought to evaluate factors influencing genetic consultations in AYA patients diagnosed with sarcoma at the University of Wisconsin (UW).

Methods: Retrospective chart review was performed on AYA patients diagnosed with sarcoma between the ages of 15-39 years, who were seen at least once in 2019 at UW. Chart review identified discussions regarding genetics, referral to genetics, genetic consultation, and results of genetic testing. Variables hypothesized to affect patient referrals for genetic consultation were identified *a priori* and included: age at diagnosis, race, ethnicity, metro versus non-metro residence as per Rural-Urban Continuum Code (RUCC), insurance and Medicaid status, localized versus metastatic cancer at time of diagnosis, receipt of chemotherapy, and documentation of a genetics discussion with an oncology provider. Age at diagnosis was divided into early young adulthood (15-18 years) and young adulthood (19-39 years) to account for potential differences in AYA patients treated by pediatric versus adult oncology providers. Categorical data was assessed using Fisher's exact tests and continuous variables were compared using one-way analysis of variance (ANOVA).

Results: We identified 43 AYA patients with sarcoma. Only 10 of these patients (10/43, 23%) had documentation of a discussion about genetics, nine of whom were subsequently referred for genetic consultation (9/43, 21%). Of the nine patients referred to genetics, six were seen in consultation (6/9, 67%). All six patients seen by genetics (6/6, 100%) underwent genetic testing, with four patients with identified heritable cancer predisposition syndromes (4/6, 67%). Syndromes identified included: neurofibromatosis type 1, hereditary paraganglioma-pheochromocytoma syndrome, familial adenomatous polyposis, and Li-Fraumeni syndrome. Table 1 details genetics referrals based on patient characteristics. A statistically significant increased likelihood for genetics referral was seen in patients who had a documented genetics discussion with an oncology provider and those with Medicaid. A higher percentage of patients referred to genetics fell into the early young adulthood age range with 38% of patients aged 15-18 years referred to genetics as compared with 17% of patients aged 19-39 years, although this was not statistically significant likely due to the small sample size.

Conclusion: Despite data to support genetic consultations in all AYA patients with sarcoma, less than 25% of such patients at our institution had a documented discussion about genetics. Almost all patients with such documentation were ultimately referred to genetics, supporting this as a critical component of the comprehensive initial assessment of all AYA patients with sarcoma. Supportive of the need for genetic consultations in these patients, all patients referred to genetics met criteria for genetic testing and 67% of patients who underwent genetic testing were found to have a heritable cancer predisposition syndrome. This data highlights the need for specific, national recommendations for the genetic evaluation of all AYA patients with sarcoma. Our study also highlights socioeconomic health disparities that should be considered as no patients who identified as Black or Hispanic or lacked health insurance were referred to genetics. Finally, consideration of pediatric models for genetic referrals should be considered given the higher percentage of patients referred to genetics in the early young adulthood age range.

Factors Affecting Genetics Referrals of AYA Patients with Sarcoma

Patient Characteristics	Total N = 43	Referred to Genetics N = 9	Not Referred to Genetics N = 34	P
Age at Diagnosis, mean (SD)	26.3 (6.9)	24 (5.8)	27 (7.2)	0.26
Age Category at Diagnosis, n (%)				
Early Young Adulthood (15-18y)	8 (18.6)	3 (33.3)	5 (14.7)	0.33
Young Adulthood (19-24y)	35 (81.4)	6 (66.7)	29 (85.3)	
Race, n (%)				
White	41 (97.6)	9 (100)	32 (97.0)	1.0
Black	1 (2.4)	0 (0)	1 (3.0)	
Ethnicity, n (%)				
Hispanic	2 (4.6)	0 (0)	2 (5.9)	1.0
Non-Hispanic	41 (95.4)	9 (100)	32 (94.1)	
RUCC Grouping, n (%)				
Metro (RUCC 1-3)	27 (62.8)	6 (66.7)	21 (61.8)	1.0
Non-metro (RUCC 4-9)	16 (37.2)	3 (33.3)	13 (38.2)	
Insurance, n (%)				
Yes	41 (95.4)	9 (100)	32 (94.1)	1.0
No	2 (4.6)	0 (0)	2 (5.9)	
Medicaid, n (%)				
Yes	7 (16.3)	4 (44.4)	3 (8.8)	0.026*
No	36 (83.7)	5 (55.6)	31 (91.2)	
Metastatic at Diagnosis, n (%)				
Yes	7 (16.3)	2 (22.2)	5 (14.7)	0.62
No	36 (83.7)	7 (77.8)	29 (85.3)	
Chemotherapy, n (%)				
Yes	29 (67.4)	7 (77.8)	22 (64.7)	0.69
No	14 (32.6)	2 (22.2)	12 (35.3)	
Genetics Discussion Documented, n (%)				
Yes	10 (23.3)	9 (100)	1 (2.9)	<0.001*
No	33 (76.7)	0 (0)	33 (97.1)	

*Statistically significant at $p<0.05$

Poster #064 3457423

RETROSPECTIVE ANALYSIS OF 18 YEARS OF TREATMENT OF MYXOFIBROSARCOMAS IN THE NETHERLANDS

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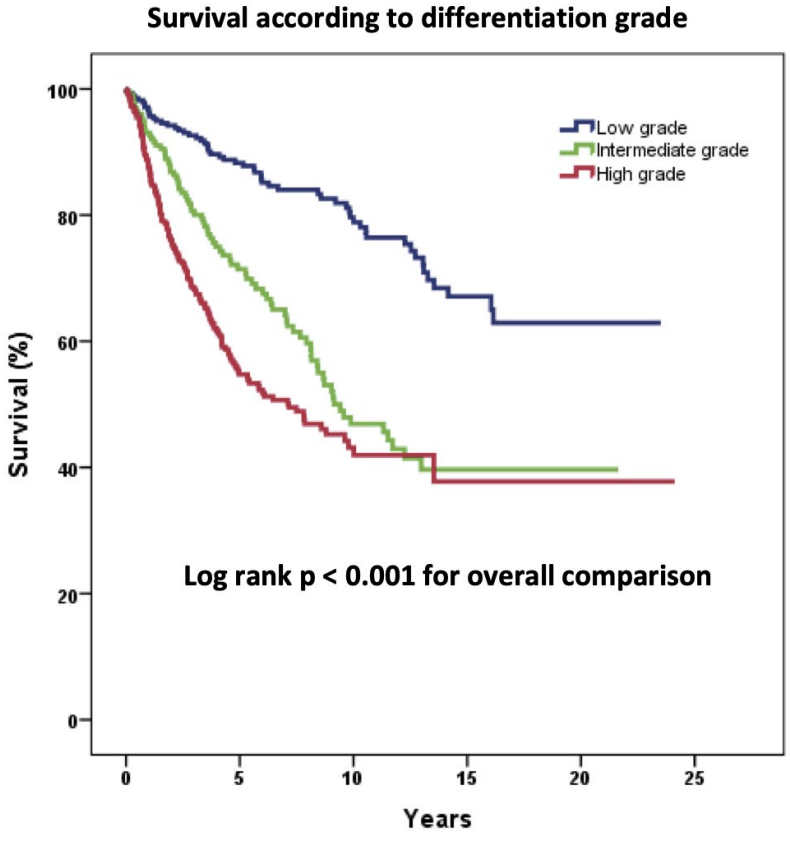
Objective: Myxofibrosarcomas (MFS) represents about 5% of soft tissue sarcoma diagnosis. It is characterized by a diffusely infiltrative pattern and therefore has a significant tendency for local recurrence while the overall prognosis is better, compared to other complex sarcomas. Since MFS is a rare entity within soft tissue sarcomas, limited data is available on long term prognosis.

Methods: Patients with a histological diagnosis of myxofibrosarcomas between 1 January 1989 and 31 December 2017 in the Netherlands were selected from the Netherlands Cancer Registry (NCR). Baseline characteristics were obtained, including tumour characteristics, type of hospital, treatment and vital status. Vital status was extracted form the nationwide GBA registry, which holds information on all Dutch inhabitants since October 1994. Follow up was completed at January 31st, 2019. Survival was calculated using Kaplan Meier estimates.

Results: Between 1 January 1989 and 31 December 2017, 944 patients were diagnosed with myxofibrosarcoma, including 950 tumours. 513 patients were male (54.3%) and median age was 65 years (interquartile range 4 to 98 years). Preoperative and postoperative radiotherapy were applied in 1.8% and 14.7%, respectively. 37% of patient underwent radiotherapy without surgery. 59% of the patients were treated in a university hospital. Median time of follow-up was 5.0 years (interquartile range 2.4 to 9.9 years) Overall survival at 5- and 10-year follow-up were 70.1% and 57.0%, respectively. A significant difference in survival was observed between low-grade MFS and high-grade MFS (log rank p<0.01), even after adjustment for age. Tumour location (extremity versus non-extremity) did not have a statistically significant effect on long-term prognosis.

Conclusion: In the largest cohort to date of patients with myxofibrosarcomas, a significant difference in survival was observed between low-grade MFS and high-grade MFS. Tumor grade was an independent predictor of long-term survival, irrespective of age.



Poster #065 3457767

OUTCOMES OF PATIENTS WITH SARCOMA AND COVID-19: A SINGLE INSTITUTION EXPERIENCE

Michael J. Wagner[1], *Seth Pollack*[2], *Lee D. Cranmer*[1], *Matthew J. Thompson*[3], *Shannon Maxwell*[1], *Stephanie Wright*[1], *Petros Grivas*[1], *Nicole Kuderer*[3], *Gary Lyman*[4], *Elizabeth T. Loggers*[2]
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Objective: COVID-19, the disease caused by novel coronavirus SARS-CoV-2, has dramatically changed oncologic practice. The first reports of patients (pts) infected with SARS-CoV-2 identified cancer as a significant negative prognostic indicator. Outcomes for pts with sarcoma and COVID-19 are unknown. We aimed to determine the course of COVID-19 in pts with sarcoma and identify factors associated with adverse outcomes.

Methods: This is a single institution retrospective study. Eligible pts were adults, had positive SARS-CoV-2 test, and known diagnosis of sarcoma. Demographic data, sarcoma specific factors including histology, extent of disease and treatment history, and COVID-19 course were evaluated. Descriptive statistics were used.

Results: To date, 9 pts [4 men; median age 60 (range 24-69)] were identified; sarcoma subtypes included uterine and non-uterine leiomyosarcoma, well-differentiated liposarcoma, myxofibrosarcoma, giant cell tumor of bone, chondrosarcoma, desmoplastic small round blue cell tumor, pleomorphic rhabdomyosarcoma, and gastrointestinal stromal tumor; 5 pts (56%) were hospitalized; 2 pts (22%) received care in intensive care unit but none were intubated; 4 pts (44%) were receiving systemic therapy when diagnosed with COVID-19 and 5 (56%) were in surveillance. For 6 pts (67%) who had received systemic therapy the time between last systemic treatment dose and COVID-19 diagnosis was 6-1820 days (median 60 days) and 6-41 days (median 20 days) in pts who died. For 5 pts (56%) who received radiation (RT) the time between RT and COVID-19 diagnosis was 20-5764 days (median 62 days) and 20-62 days (median 28 days) for patients who died. For 6 pts (67%) who received surgery the time between surgery and COVID-19 diagnosis was 44-4538 days (median 376 days); 2 patients who died had surgery 87 and 268 days before COVID-19 diagnosis, respectively. Lab values were available for 5 pts. Total WBC at time of COVID-19 diagnosis was 0.97-13.3. All 3 pts with available data were lymphopenic (absolute lymphocyte count 0.08-0.95) and one was neutropenic (absolute neutrophil count 0.79). 2 pts died from COVID-19 complications. A third patient died from progressive sarcoma, but tested SARS-CoV-2 positive on routine screening prior to a procedure and a potential role of COVID-19 in the death cannot be excluded. The overall case fatality rate was 33%. All 3 pts who died were receiving gemcitabine-based chemotherapy at the time of SARS-CoV-2 diagnosis and had received at least one other prior line of cytotoxic chemotherapy.

Conclusion: Pts with sarcomas may be at particular risk for adverse COVID-19 outcomes. More efforts to capture outcomes for a larger cohort with sarcoma are urgently needed to clarify COVID-19 risks and patient risk factors to better tailor therapy during the SARS-Cov-2 pandemic. We plan to expand this cohort by fostering multi-site collaborations, including with CCC19.

Poster #066 3457998

DECISIONAL CONTROL PREFERENCES IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMAS STARTING 1ST LINE PALLIATIVE CHEMOTHERAPY: RESULTS FROM THE HOLISTIC STUDY

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Objective: Treatment decisions in the setting of advanced soft tissue sarcoma (STS) are often complex due to limited treatment options and poor prognosis. Although shared decision-making is acknowledged to be an important component of patient-centred care, little is known about the preferences of patients with advanced STS for participation in treatment decisions. Our principal aims were to assess patients' preferred and actual roles in treatment decisions.

Methods: The HOLISTIC study is a prospective cohort study in the UK and The Netherlands assessing health-related quality of life (HRQoL) in advanced STS patients receiving palliative chemotherapy. Participants completed a questionnaire before starting 1st-line chemotherapy, including the control preference scale (CPS); a validated tool (English and Dutch) to measure patients preferred and actual role in treatment decision-making. Chi-squared and Fisher's exact tests were used to evaluate associations between preferred role, actual role and concordance/discordance in treatment decisions, and patient characteristics, HRQoL (summary score of EORTC QLQ-C30) and healthcare system (UK and The Netherlands).

Results: In total, 137 patients with advanced STS participated (UK: n=72, Netherlands: n=65). Median age was 62 (range 27-79) years. Patients most commonly preferred a 'collaborative' role (n=59, 43%), where the patient and doctor share responsibility in treatment decisions, or an 'active-collaborative' role (n=35, 26%), where the patient makes the final decision after considering their doctor's opinion. A smaller proportion of patients preferred a 'passive-collaborative' role (n=25, 18%), where the doctor makes the final decision after considering the patient's opinion. A minority preferred to make the decision themselves (active role: n=10, 7%) or to leave decisions to their doctor (passive role: n=6, 4%); two patients did not answer. Actual roles in decisions about treatment were similar to preferred roles; most commonly collaborative (n=54, 39%), 'active-collaborative' (n=38, 28%) or 'passive collaborative' (n=29, 21%). A minority reported having an active role (n=8, 6%) or a passive role (n=8, 6%). Discordance between preferred role and actual role was observed in around one quarter of patients (n=33, 24%); most commonly patients who preferred a collaborative role but had an active-collaborative role (n=9) in actual treatment decisions.

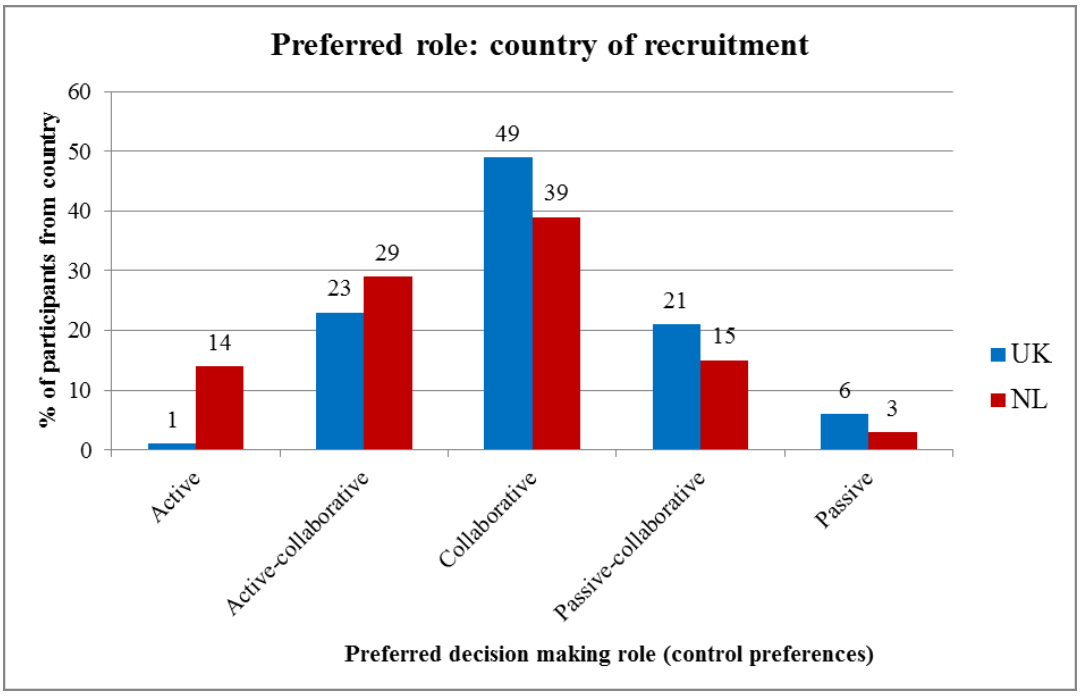
Preferred role in treatment decisions was significantly associated with country of recruitment (p=0.043; Figure1). Dutch participants most commonly preferred an active or active-collaborative role (43%) whereas UK participants preferred a collaborative role (49%). Females more commonly preferred a collaborative approach compared to men (55% vs. 32%), however this trend did not reach statistical significance (p=0.051). Actual role in treatment decisions was significantly associated with country of recruitment (p=0.005), gender (p=0.022) and performance status (p=0.026) (Table 1). Preferred and actual roles in treatment decisions were not associated with age, ethnicity, relationship status, educational level, HRQoL, disease extent (locally-advanced vs. metastatic) or time period since diagnosis of advanced STS. Discordance between preferred and actual roles was not associated with patient characteristics, HRQoL or country of recruitment.

Conclusion: The majority of patients with advanced STS preferred a collaborative approach to treatment decisions; however, Dutch participants preferred a more active role in decisions compared to UK participants. Cultural differences and healthcare system factors should be explored further, and considered during challenging treatment discussions. Gender and performance status also influenced actual role in treatment decisions. Our findings support a personalised decision-making approach, taking into account the preferred role of STS patients in treatment decisions in the palliative setting.

Table 1: Factors associated with preferred or actual role in treatment decisions

PREFERRED ROLE IN TREATMENT DECISIONS (control preferences)						
Variables	Active n (%)	Active-collaborative n (%)	Collaborative n (%)	Passive-collaborative n (%)	Passive n (%)	p-value
Country UK NL	1 (1) 9 (14)	16 (23) 19 (29)	34 (49) 25 (39)	15 (21) 10 (15)	4 (6) 2 (3)	**0.043**
Gender Male Female	7 (10) 3 (5)	18 (27) 17 (25)	22 (32) 37 (55)	17 (25) 8 (12)	4 (6) 2 (3)	0.051
ACTUAL ROLE IN DECISION ABOUT PALLIATIVE CHEMOTHERAPY						
Variables	Active n (%)	Active-collaborative n (%)	Collaborative n (%)	Passive-collaborative n (%)	Passive n (%)	p-value
Country UK NL	1 (1) 7 (11)	14 (19) 24 (37)	37 (51) 17 (26)	16 (22) 13 (20)	4 (6) 4 (6)	**0.005**
Gender Male Female	6 (9) 2 (3)	19 (28) 19 (28)	18 (27) 36 (52)	20 (29) 9 (13)	5 (7) 3 (4)	**0.011**
Performance status ECOG 0 ECOG 1 ECOG 2	1 (2) 4 (5) 1 (14)	10 (22) 18 (24) 5 (71)	26 (57) 27 (36) 0 (0)	7 (15) 20 (27) 1 (14)	2 (4) 6 (8) 0 (0)	**0.026**

Figure 1: Preferred role according to country of recruitment



Poster #067 3458044

IMRIS: A PHASE II STUDY OF INTENSITY MODULATED RADIOTHERAPY (IMRT) IN EXTREMITY SOFT TISSUE SARCOMA (STS)

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Objective: Primary STS are rare tumours, with many occurring in the extremities. Local management of these tumours is limb-sparing surgery, with neo-adjuvant or adjuvant radiotherapy (RT) for patients at high risk of local recurrence. The purpose of this trial was to establish if the use of IMRT in extremity STS would reduce late normal tissue toxicity compared with historical use of 3D-conformal RT (3D-CRT).

Methods: This phase II trial (A'Hern's single stage phase II design) was conducted in 18 sites, with two treatment cohorts: IMRT 50 Gy in 25 fractions (neoadjuvant prior to surgery) or 60/66 Gy in 30/33 fractions adjuvant (after R0/R1 resection). Eligibility criteria were: STS of upper or lower limb/limb girdle, requiring (neo)adjuvant RT, no previous RT to the same site, WHO performance status (PS) 0-2, age ≥16 years. All patients gave written informed consent. Primary endpoint was rate of ≥ grade 2 late soft tissue fibrosis at 2 years (any assessment between 21 & 27 months) after completion of IMRT as assessed by RTOG late radiation morbidity scoring system (subcutaneous tissue). Based on 85% power, 1-sided 5% alpha, a historical rate of 30% with conventional 3DCRT [unpublished single institutional data, UCH], an expected 10% reduction with IMRT and a 17% dropout, the recruitment target was 167 patients. Secondary endpoints were to explore incidence and pattern of acute and late radiotherapy related toxicity, to assess the impact of IMRT on function and quality of life (using WHO PS, EORTC QLQ-C30, Toronto Extremity Salvage Score (TESS) and Musculoskeletal Tumor Society Rating scale (MSTS)), to describe overall survival and disease-free survival, and to establish incidence and severity of wound complications.

Results: Between March 2016 and July 2017 168 patients were registered. Eight patients did not received RT and were not included in the analysis. 63% of patients were male; median age was 58 years. The median maximum tumour diameter was 75mm. Of 160 patients receiving radiotherapy, 106 (66%) received neoadjuvant and 54 (34%) received adjuvant radiotherapy, with median RT doses of 50Gy and 60Gy respectively. Median follow up was 33.1 months (IQR: 29.8 – 36.0). At 2 years, overall survival rate was 83.4%, and disease-free survival rate was 65.5%. Of 102 patients assessable for the primary endpoint, 12 (11.8%, 90%CI: 6.9% to 18.4%) had ≥ grade 2 subcutaneous tissue toxicity at 2 years. Toxicity of ≥ grade 2 for skin, bone, joint and oedema (Stern's scale) at 2 years were observed in 7/103 (6.8%), 3/104 (2.9%), 10/104 (9.6%) and 5/104 (4.8%) patients respectively. Acute skin toxicity (RTOG) ≥ grade 2 was observed in 46 (28.8%) of patients, more frequently in patients receiving adjuvant (23, 42.6%) than neoadjuvant (23, 21.7%) RT. Global health status ($p=0.045$), social ($p=0.008$) and emotional functioning ($p<0.001$) increased with time over 30 months after RT, but physical functioning decreased with time ($p=0.018$). There was no evidence of a time effect for WHO status, or for other QLQ-C30, TESS and MSTS dimensions ($p>0.05$). More surgical adverse reactions were observed following neoadjuvant than adjuvant RT (56, 53% vs 20, 37%), and also more wound complications were observed with neoadjuvant than adjuvant RT (22% vs 9%), with readmission for wound care, and 2nd surgery for wound repair in 8.5% vs 1.9%, and 14.2% vs 0%, respectively.

Conclusion: We have shown a rate of ≥ grade 2 subcutaneous tissue toxicity at 2 years after IMRT of 11.8%, which represents a significant reduction compared with a 30% historical rate after 3DCRT. Similarly low rates of skin, joint and bone late toxicity were observed at 2 years. This study provides further evidence that IMRT for extremity STS results in less late normal tissue toxicity at 2 years than previous treatments with 3DCRT.

Poster #068 3458250

GENETIC MODELS REVEAL THAT THE NOVEL *VGLL2-NCOA2* FUSION ONCOGENE LEVERAGES EMBRYONIC PROGRAMS FOR SARCOMAGENESIS

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Objective: Rhabdomyosarcoma (RMS) is an aggressive pediatric cancer characterized by a misregulation of skeletal muscle developmental pathways. To date, identified oncogenic drivers predominantly include *RAS* mutations or chromosomal translocations and gene fusions between *PAX3* or *PAX7* and *FOXO1*. RNAseq analysis of sarcomas with non-canonical mutations or gene fusions has identified new potential genetic drivers of tumorigenesis that have not been functionally validated for their transformation capacity and biological activity. One such new fusion is a chromosomal translocation and inversion between chromosomes 6 and 8, which acts to juxtapose two transcriptional co-activators, *VGLL2* and *NCOA2*. This *VGLL2-NCOA2* fusion was identified in congenital rhabdomyosarcoma clinical cohorts by us and others, and characterizes RMS-like tumors that express MYOD and MYOG histological markers. However, evidence of *VGLL2-NCOA2* transformation capacity has not been verified, hindering insights into its functional contributions to tumorigenesis and identification of novel therapeutic opportunities.

Methods: Here, we interrogate the function of *VGLL2-NCOA2* using complementary genomic patient data and zebrafish model systems. We utilized the Tol2 transposon system to insert human *VGLL2-NCOA2* into the zebrafish genome and express it during zebrafish development in a variety of cellular contexts. Mosaic expression of human *VGLL2-NCOA2* generated tumors that were analyzed histologically and via RNAseq to verify their similarity with the human disease. Given the developmental nature of the disease, we also compared gene expression signatures from tumors, mature skeletal muscle, and embryonic muscle. We found a sub-set of genes that were expressed only in immature muscle and tumor contexts, underscoring shared molecular features of development and tumorigenesis.

Results: We found that *VGLL2-NCOA2* is sufficient for tumorigenesis and results in aggressive tumors with high penetrance by 75 days of age in zebrafish. Further, the histology of zebrafish tumors resembles the human disease, and tumors express markers indicative of RMS, such as *myog* and *desma*. A cross-species RNAseq analysis of patient and zebrafish *VGLL2-NCOA2* tumors highlights a significant enrichment and overlap between gene expression signatures. Finally, mapping the gene expression signatures of *VGLL2-NCOA2* zebrafish tumors along the spectrum of zebrafish embryogenesis indicates a clustering with developmental stages corresponding to early somitogenesis, emphasizing their arrested developmental features, and identifying signaling pathways that are reactivated or inappropriately persist during the tumorigenic process.

Conclusion: We have generated the first animal model of human *VGLL2-NCOA2* tumorigenesis, and have applied our model to understand disease biology and to identify potential therapeutic targets. Our studies highlight the power of integrating patient genomic data with vertebrate zebrafish systems for the study of rare, fusion-driven pediatric sarcomas.

Poster #069 3458308

CONTEMPORARY OUTCOMES AND SECONDARY AMPUTATION AFTER LOCAL RECURRENCE IN PATIENTS AFFECTED BY EXTREMITY SOFT TISSUE SARCOMA TREATED WITH LIMB-SPARING SURGERY AT A REFERENCE INSTITUTION

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Objective: Local recurrence (LR) after limb-sparing surgery in patients with extremity soft tissue sarcomas (ESTS) represents a challenge. This study reviewed data of contemporary ESTS patients who developed LR to analyse the rate of further LR, treatment approaches, and post-relapse outcomes.

Methods: Data of primary ESTS who underwent limb-sparing surgery between 2008 to 2017 at a sarcoma reference unit were extracted from a prospectively maintained database. Patients who underwent primary amputation, WDLPS, DFSP and desmoids were excluded. Differences in treatment patterns of LR over time (first period 2008-2012, second period 2013-2017) were investigated, as well as post-relapse outcomes.

Results: Overall 1,084 patients were treated for primary ESTS, among which 18 (1.3%) patients had primary amputation. After a median follow up of 61 months (95%CI 35-88), 85/1,084 developed a LR (7.8%) (Figure 1).

Commonest histology was MFS 24 (28.2%), followed by UPS 15 (17.6%) (Figure 2). Most patients had a G2 (N=26, 30.5%) and a G3 (N=56, 65.8%) sarcoma, respectively. Recurrence was multifocal in 26 patients (30.6%) and ulcerated in 5 (5.9%); metastatic disease was present at the time of LR in 25 (29.4%), while it developed afterwards in 21 (24.7%). 61/85 (71.8%) patients were treated with surgery, of them 50 had wide excision (in 20 plastic reconstruction was needed) and 11 (12.9%) had an amputation, leading to a secondary amputation rate of 1% (N=11/1,066) and an overall amputation rate of 2.3% (N=29/1,084) at time of 1st LR. Microscopic surgical margins (available for 57/61 patients) were R0, R1, and R2 in 45 (78%), 12 (22%), and 0 (0%), respectively. Postoperative morbidity was 21.3% (Clavien-Dindo grade ≥3). Radiotherapy was performed in 26/85 (30.6%) patients, including 23 patients who underwent surgery (18 preoperatively, 5 postoperatively and 3 as definitive treatment). Seven patients (8.4%) had a TNF-based isolated limb perfusion before surgery for LR. Systemic chemotherapy for LR was performed in 33/85 (38.8%) patients, of them 21 underwent also surgery (18 preoperatively, 1 postoperatively, 2 pre and postoperatively). After a median post-recurrence follow up of 50 months (95%CI 20-63), 5-year post-recurrence LR (LRFS) and distant metastasis-free survival (DMFS) was 73% (55-88%) and 42% (29-54%), respectively. 5-year post-relapse overall survival (OS) was 56% (95%CI 42-68%). In the first and second study period – after 62 months (95%CI 52-86) and 24 months (95%CI 9-50) median follow up, respectively –, 5-yr post-recurrence LRFS, DMFS and OS were 71% (49-84%) and 82% (50-94%) (P=0.13), 41% (26-56%) and 49% (29-65%) (P=0.02), 55% (38-70%) and 63% (42-78%,P=0.02), respectively.

A 2nd LR was detected in 13/61 (21.3%) patients who underwent surgery: 7 patients (53.9%) had a 3rd surgical resection (1 hemipelvictomy and 6 limb-sparing procedures). Pre-operative chemotherapy was given in 2 patients, chemo-radiation in 1, ILP in 1 patient and post-operative chemotherapy in 1 patients. Three patients underwent amputation for further recurrences. Overall secondary amputation rate was 17.6% (N=15/85) for those who recurred (3.0%, N=33/1084, final secondary amputation rate for primary ESTS). There were no changes in treatment patterns over the first and second study period with respect to use of surgery and perioperative therapies. In the second period, no amputation for 1st LR was performed.

Conclusion: LR was 8% after limb sparing surgery for ESTS. Although overall secondary amputation rate is 3%, this figure climbs to 17.6% for those who developed LR. Even if RT and CT have been largely adopted as perioperative treatments in recurrent ESTS, post-relapse outcomes remain poor. These data could serve as a benchmark for studies focusing on innovative and effective treatments.

Figure 1. Consort diagram

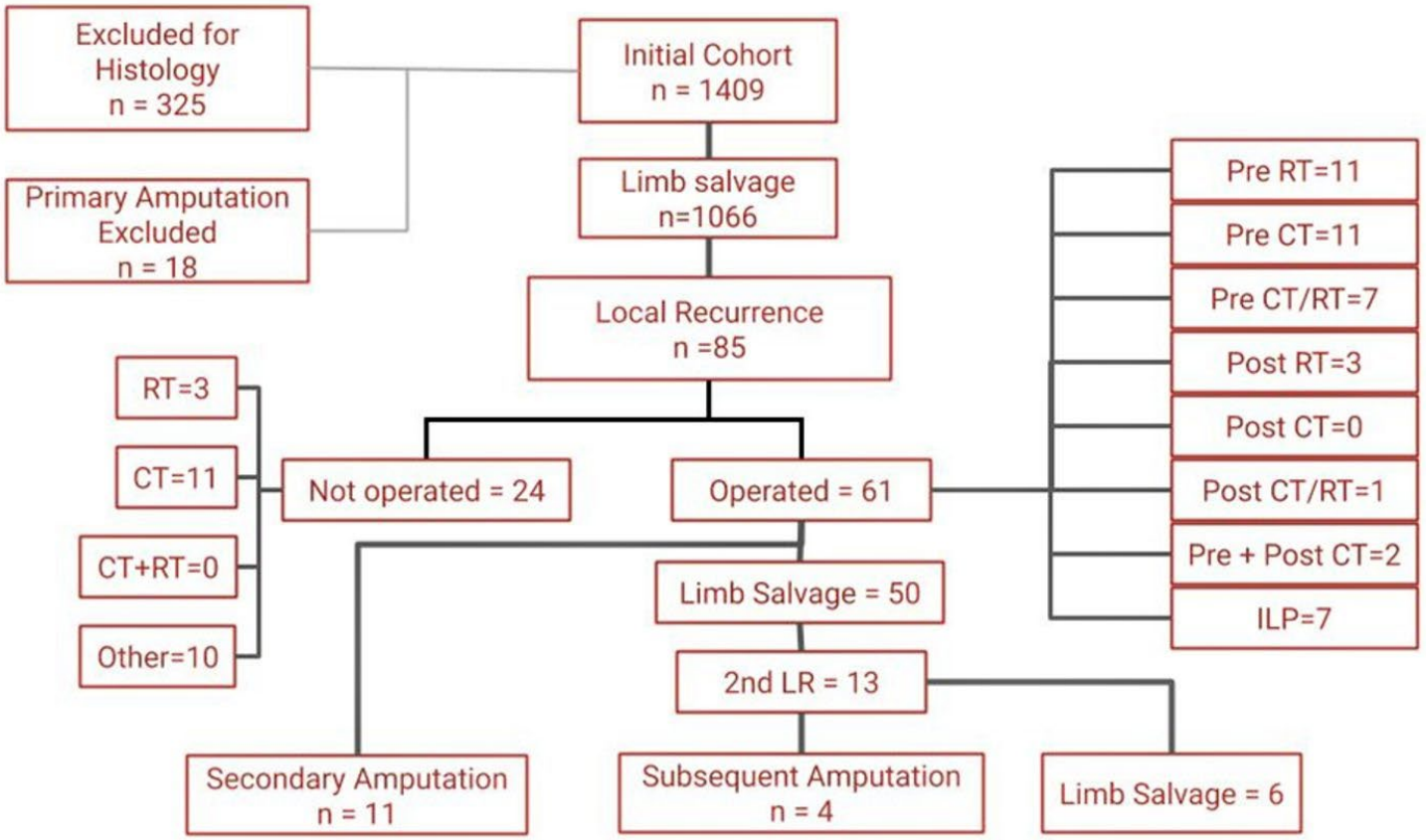
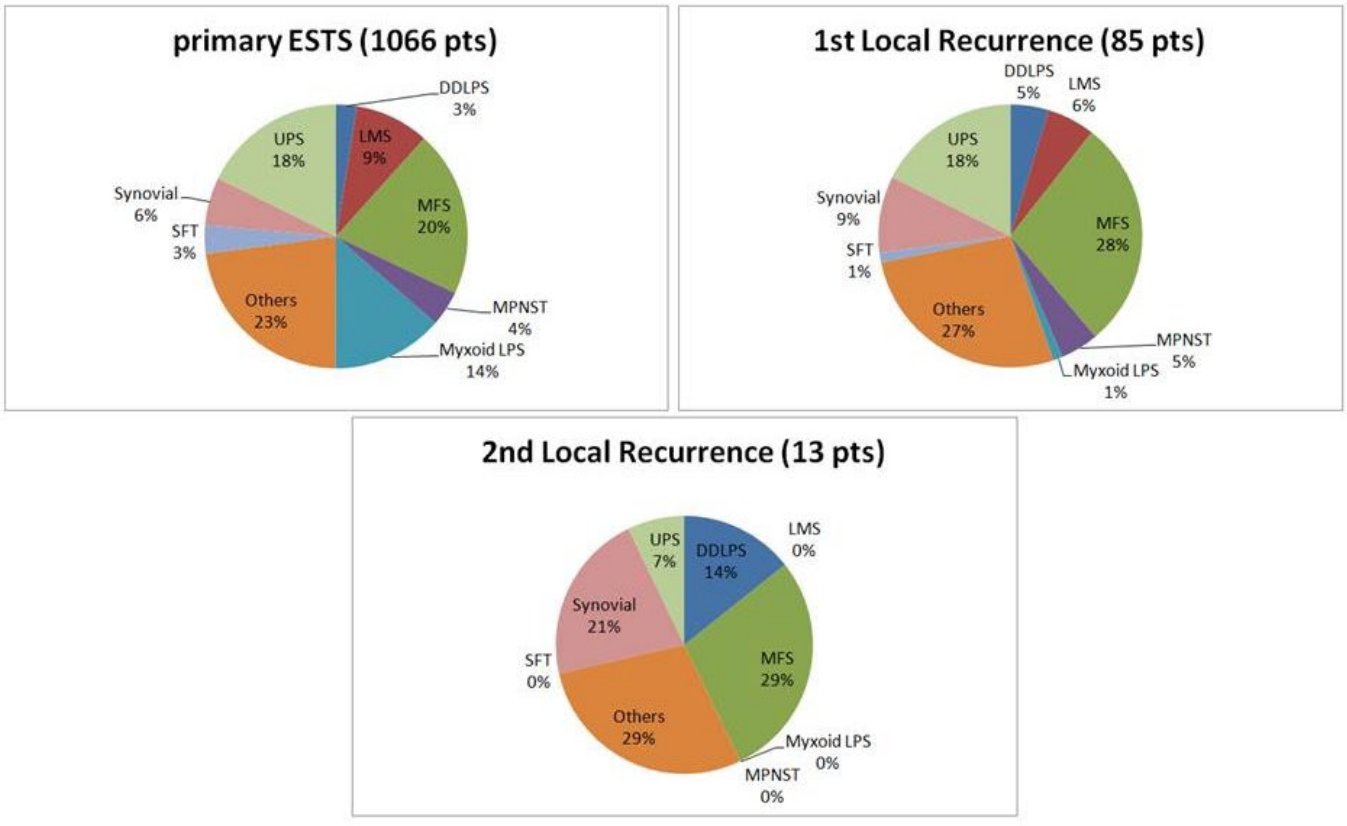


Figure 2. Histology distribution in primary ESTS, 1st and 2nd LR



Poster #070 3458516

HARNESSING THE ELECTRONIC MEDICAL RECORD TO IMPROVE THE EVALUATION OF SOFT TISSUE MASSES IN THE PRIMARY CARE SETTING: A PILOT STUDY ON THE IMPACT OF A BEST PRACTICE ALERT

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Objective: Inappropriate evaluation of soft tissue masses (STM) may lead to a delay in diagnosis of soft tissue sarcomas (STS) because these neoplasms are often mistaken for more common, benign conditions. Current guidelines recommend magnetic resonance imaging (MRI) for STMs greater than five centimeters in size or lesions that are enlarging, painful, or deep. Best Practice Alerts (BPA) have emerged as a form of artificial intelligence built into the electronic medical record (EMR) that serve to improve patient care and decrease healthcare costs, yet they may be intrusive to clinicians in a busy practice setting. We developed a BPA at HealthPartners, a Minnesota-based integrated healthcare delivery system that uses EPIC EMR, and linked it to ICD-10 diagnosis codes associated with STMs. The BPA prompted primary care providers (PCP) on appropriate STM evaluation. We then conducted a pilot project that assessed clinician acceptance of the BPA, its effect on improving PCP confidence in evaluating STMs, and its impact on patient care.

Methods: We attached a BPA to specific ICD-10 diagnosis codes associated with STMs to prompt PCPs on suggested use of MRI for further evaluation. We surveyed PCPs and assessed their baseline demographics, familiarity with STS, and acceptance of the BPA as a clinical decision-making support tool. A 10-point Likert scale was used to assess changes in clinician confidence levels with STM evaluation before and after interacting with the BPA. We assessed impact on patient care by determining how many MRI scans were completed as a result of the BPA as well as the associated clinical outcomes.

Results: Seventy-three PCPs at five different HealthPartners primary care clinics interacted with the BPA each over a three-month period of time. Forty-two clinicians (58%) completed a post-BPA survey and twenty-four (33%) completed both a pre- and post-BPA survey. The BPA significantly improved PCP confidence levels when evaluating STMs ($p = 0.0001$), and 75% of clinicians agreed or strongly agreed that the BPA enhanced their awareness of STS with 70% more likely to consider a STS diagnosis after viewing the BPA. A total of 803 BPAs were triggered (average per month = 100.4) on a total of 631 patients (average per month = 78.9). A clinician saw the BPA an average of 3.8 times per month. Seventeen MRIs were completed as a result of the BPA (average per month = 1.9). Four malignant or potentially malignant diagnoses were identified (23.5%), while lipoma was the most common non-malignant diagnosis (23.5%).

Conclusion: This pilot study linked a BPA to certain ICD-10 codes associated with STMs to prompt MRI evaluation for large or enlarging, painful, or deep masses. Seventeen MRIs were completed and four malignant or potentially malignant diagnoses were identified. PCPs found the BPA to be a useful clinical decision-making support tool, and it improved their confidence level when evaluating STMs. A larger healthcare system-wide project is planned.

Poster #071 3458545

TUMOR RESPONSE TO WINDOW THERAPY WITH TEMSIROLIMUS, IRINOTECAN, AND TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED HIGH-RISK EWING SARCOMA; A PHASE II SINGLE INSTITUTION STUDY

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Objective: Despite aggressive multi-modal therapy, patients with Ewing sarcoma (ES) presenting with a pelvic primary tumor, older age, or metastatic disease continue to have a poor outcome. The combination of irinotecan (IRN) and temozolomide (TMZ) has shown activity in ES. Additionally, ES has demonstrated sensitivity to mTOR pathway inhibition. The primary objective of ESFT13 (NCT01946529) was to estimate the tumor response rate to two initial courses of IRN, TMZ and temsirolimus (TEM) in newly-diagnosed patients with high-risk ES.

Methods: Patients with newly-diagnosed ES who were ≥14 years old, or had metastatic disease, or had a pelvic primary tumor, and did not require emergent radiotherapy were eligible to receive two courses (21 days duration) of TEM (35 mg/m^2 IV, days 1 and 8) in combination with a low-dose protracted course of IRN (20mg/m^2 IV, daily x 5 days x 2) and TMZ (PO 100 mg/m^2 x 5 days). After the window therapy, patients received standard of care with interval-compressed vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide, followed by maintenance therapy. Local control was performed at week 19. Magnetic resonance imaging (MRI) and positron emission tomography (FDG PET/CT) scan was performed at baseline and 6 weeks. Changes in total tumor volume (MRI) and standardized uptake values (SUV) in the primary tumor were assessed; however, this was not used to determine response. The primary endpoint of the study was defined as tumor response as assessed by the WHO criteria (sum of the products of the maximum perpendicular diameters) at the end of window therapy (week 6). A two-stage sequential design was used with a planned accrual of 23 patients to detect a >50% response to window therapy (CR or PR) with 80% power; 7/12 responses were required at interim analysis to continue the study.

Results: Thirteen patients received window therapy. The median age at enrollment was 11.8 years (6.6 – 23.5). Nine patients had metastatic disease (3 lung only), 6/13 were ≥ 14 yo, and 3/13 had pelvic primaries. The 4/13 with non-pelvic localized disease were high-risk due to age. There were 12 patients evaluable for response to window therapy at interim analysis; 2/12 had partial resection performed prior to evaluation. No grade > 3 toxicities occurred during window therapy: 9/13 experienced at least 1 grade 3 toxicity. All patients recovered from their toxicities: 4 required interruptions in therapy, 1 required a dose reduction, and 1 discontinued therapy. The most common grade 3 adverse events were hyponatremia (n = 5), colitis/diarrhea (n = 4), anemia (n = 3), hypophosphatemia (n = 3), mucositis (n = 3), and nausea (n = 3). According to WHO response criteria, of the 12 patients evaluable for response, 3 achieved a partial response, 8 stable disease, and 1 progressive disease. All patients evaluable for MRI response had a decrease in their primary tumor volume at week 6 (n = 10) (% decrease: μ = 35.5%, σ = 17.7%, 10.2-72%). Nine patients were evaluable by PET. All patients demonstrated a decrease in PET avidity (Wilcoxon matched-pairs signed rank test: p = 0.0039) (ΔSUV_{max}: μ = 56.24%, σ = 19.27, 23-88.24) (Figure 1). Given the low response rate in the first stage, the protocol was closed to accrual. Further analysis of overall outcomes is ongoing.

Conclusion: While the combination of TEM, IRN, and TMZ did not lead to significant responses as determined by WHO criteria, all patients showed a decrease in their primary tumor SUV measurements and a volumetric decrease of their primary tumor by MRI, suggesting that activity of novel agents can be underestimated using traditional response criteria.

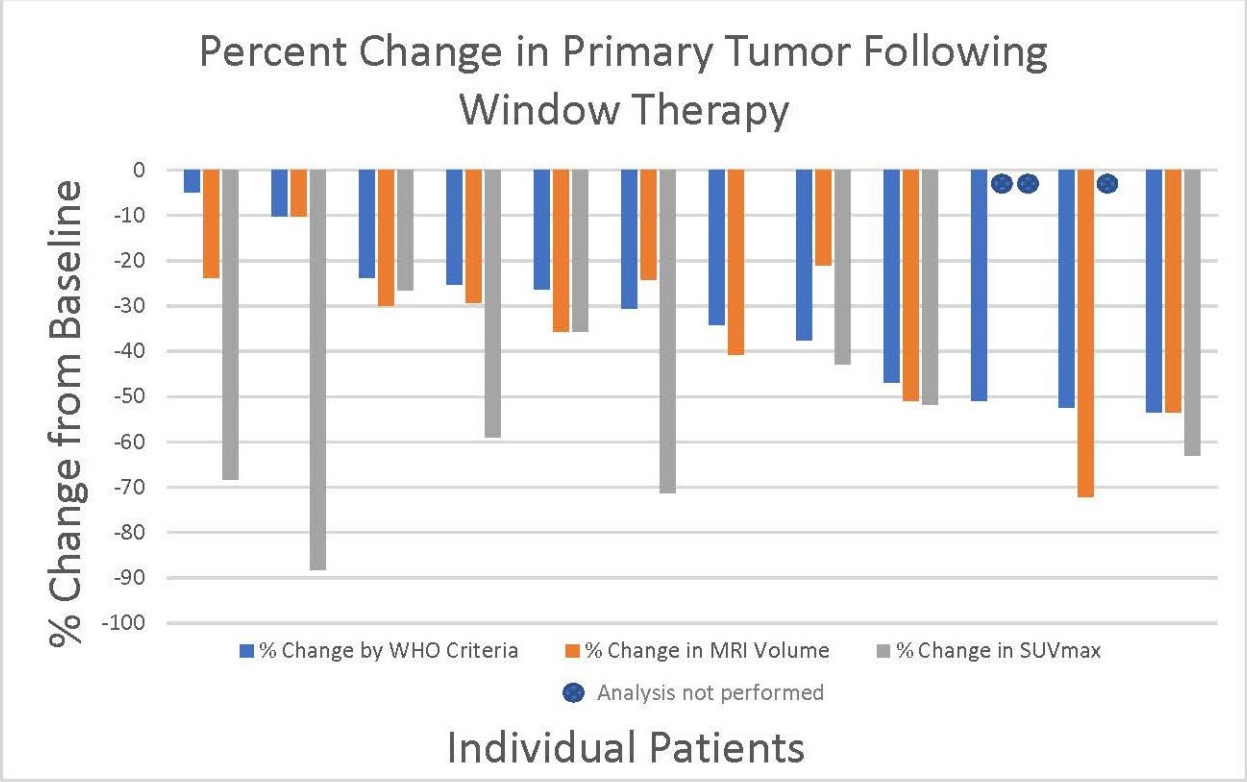

Figure 1. Waterfall diagram demonstrating % change from baseline of the primary tumor following 6 weeks of window therapy.

Poster #072 3458703

RETROSPECTIVE ANALYSIS OF THE CLINICAL PRESENTATION, TREATMENT AND OUTCOME OF ANGIOSARCOMA IN A SARCOMA REFERRAL CENTER

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Objective: Angiosarcoma (AS) is a rare, aggressive subtype of soft tissue sarcoma (STS). Treatment requires a multidisciplinary approach and should preferably be carried out in reference centers. We performed an in-depth analysis of patient characteristics, treatments and prognostic factors in patients (pts) with AS treated at the University Hospitals Leuven (Belgium).

Methods: We reviewed electronic clinical records of AS pts who were seen in our institution between 1987 and 2018, based on LECTOR, a sarcoma-specific institutional database. Demographic and clinical data collected include age at diagnosis, gender, primary tumor site, number and localization of metastatic sites, and others. AS cases were categorized in 7 different clinically relevant subtypes according to tissue of origin and underlying risk factors: radiation-induced; primary soft tissue; primary cutaneous; primary breast; primary bone; lymphedema-associated; unknown primary. LECTOR also covers information on local (surgery, radiotherapy) and systemic treatments applied, and the response to systemic therapy is captured according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) based on local clinical routine assessment. The Kaplan-Meier method was used to estimate progression-free (PFS) and overall survival (OS) in the different subsets of pts.

Results: We identified 134 pts with AS, of whom 40 (30%) were classified as radiation-induced, 41 (31%) as primary soft tissue, 32 (24%) as primary cutaneous, 7 (5%) as primary breast, 6 (4%) as primary bone, 3 (2%) as lymphedema-associated and 5 (4%) as unknown primary cases. Key patient and disease characteristics, such as age, gender distribution and rate of metastasis, varied between subgroups. Synchronous metastasis was observed in 31 (23%) of pts. 52 (38.8%) pts developed metachronous metastasis after initial local treatment within a median of 9.3 mo (range, 0.7-256). In the total AS population, the median OS from first diagnosis was 17.8 mo (range, 0-300.3), and was substantially different amongst the clinical subgroups, ranging from 4.4 mo (range 1.4-6.9) in unknown primary AS to 81.7 mo (range 0-134.8) in the primary breast subset. A total of 66 (49%) pts received at least one line of systemic therapy for advanced AS, 49 (34%) a second line and 26 (19%) subsequent lines of treatment (maximum 5). The most commonly used agents in first line were doxorubicin (n=32, 48%) and paclitaxel (n=26, 39%), mainly as single agents (81%). PFS and OS were similar for these two treatments, with a PFS of 6.2 mo (range, 0.5-45.0) for doxorubicin and 4.8 mo (range, 0.4-19.2) for paclitaxel, respectively. Median OS from start of systemic therapy was 8.7 mo (range, 1.2-104.7) for doxorubicin and 10.4 mo (range, 0.5-57.1) for paclitaxel. Pts received a variety of other systemic agents in subsequent lines of treatment, the most common being pazopanib, docetaxel and ifosfamide.

Conclusion: AS is a very heterogenous sarcoma subfamily, with substantial variability in clinical presentation and survival among different patient subsets. Prognosis is generally poor, and there is no obvious difference in outcome comparing the two most frequently used chemotherapy agents in first line, paclitaxel and doxorubicin.

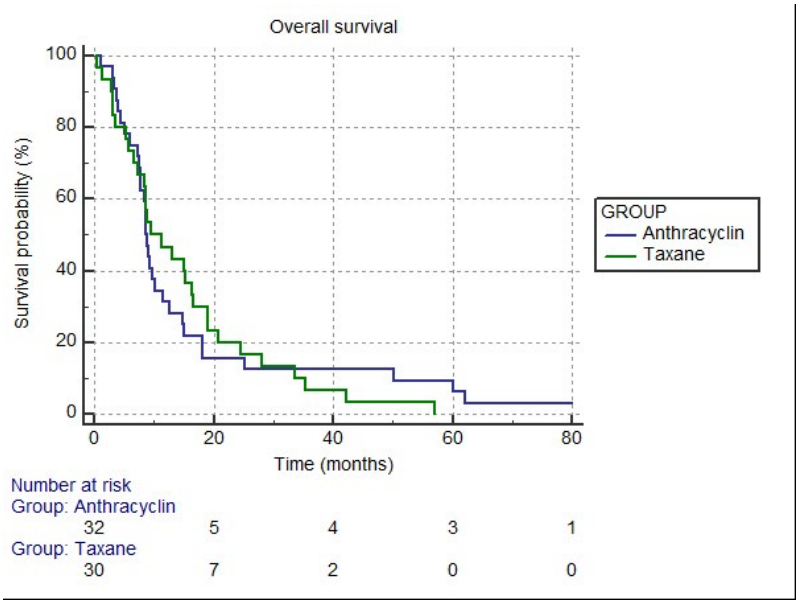
Patient characteristics according to subtype

Characteristic		All patients (n=134)	Soft tissue (n=41)	Radiation ind. (n=40)	Cutaneous (n=32)	Breast (n=7)	Bone (n=6)	UP. (n=5)	Lymphedema (n=3)
Mean age at diagnosis, years (range)		60.3 (18-90)	58 (19-85)	69 (18-90)	70.5 (18-90)	31 (25-40)	61.5 (25-77)	64 (43-69)	59 (41-80)
Gender, n (%)									
	Male	53 (39.6)	25 (61.0)	3 (7.5)	16 (50)	7 (100)	4 (66.7)	4 (80)	1 (33.3)
	Female	81 (60.4)	16 (39.0)	37 (92.5)	16 (50)	0 (0)	2 (33.3)	1 (20)	2 (66.7)
Primary tumor site, n (%)									
	Breast	39 (29.1)	0 (0)	32 (80)	0 (0)	7 (100)	0 (0)	0 (0)	0 (0)
	Head and neck	30 (22.3)	7 (17.1)	3 (7.5)	20 (62.5)	0 (0)	0 (0)	0 (0)	0 (0)
	Extremities	22 (16.4)	2 (4.9)	1 (2.5)	12 (37.5)	0 (0)	4 (66.7)	0 (0)	3 (100)
	Abdomen	20 (14.9)	18 (43.9)	1 (2.5)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)
	Thorax	18 (13.4)	14 (34.1)	3 (7.5)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)
	Unknown	5 (3.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (100)	0 (0)

Disease characteristics and outcomes according to subtype

Characteristic		All patients (n=134)	Soft tissue (n=41)	Radiation ind. (n=40)	Cutaneous (n=32)	Breast (n=7)	Bone (n=6)	UP. (n=5)	Lymphedema (n=3)
Metastasis and local relapse, n (%)									
	Local relapse	51 (38.1)	6 (14.6)	23 (57.5)	17 (53.1)	3 (42.9)	1 (16.7)	0 (0)	1 (33.3)
	Metastasis	83 (61.9)	31 (75.6)	20 (50.0)	17 (53.1)	4 (57.1)	4 (66.7)	5 (100)	2 (66.7)
	Synchronous	31 (23.1)	16 (39.0)	2 (5.0)	3 (9.4)	1 (14.3)	3 (50.0)	5 (100)	1 (33.3)
	Metachronous	52 (38.8)	15 (36.6)	18 (45.0)	14 (43.7)	3 (42.9)	1 (16.7)	0 (0)	1 (33.3)
Site of first metastasis, n (% of M+ pts)									
	Lung	39 (47.0)	13 (41.9)	10 (50)	11 (64.7)	1 (25)	2 (50)	2 (40)	0 (0)
	Bone	25 (30.1)	7 (22.6)	4 (20)	5 (29.4)	1 (25)	3 (75)	5 (100)	0 (0)
	Liver	21 (25.3)	11 (35.5)	1 (5)	4 (23.5)	2 (50)	1 (25)	2 (40)	0 (0)
	Lymph node	15 (18.1)	6 (19.4)	4 (20)	2 (11.8)	0 (0)	2 (50)	0 (0)	0 (0)
	Brain	3 (3.6)	3 (9.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mean time to first M+, months (range)		9.3 (0.7-256)	5.0 (0.7-16.7)	13.6 (2-210)	11 (0.8-256)	73 (17-110)	50.2 (50.2)	/	3.5 (3.5)
Number of sites of metastasis, n (% of M+ pts)									
	1	48 (57.8)	17 (54.8)	16 (80)	10 (58.8)	2 (50)	0 (0)	1 (20)	2 (100)
	>/= 2	35 (42.2)	14 (45.2)	4 (20)	7 (41.2)	2 (50)	4 (100)	4 (80)	0 (0)
Median overall survival, months (range)		17.8 (0-300.3)	11.3 (0.1-114.2)	29.2 (0.7-219.7)	26.2 (1.1-300.3)	81.7 (0-134.8)	11.2 (1.9-150.6)	4.4 (1.4-6.9)	5.7 (3.6-61.0)

Kaplan-Meier estimate of median overall survival (calculated from start of palliative systemic therapy) according to type first line systemic treatment.



Poster #073 3458722

POTENTIAL MOLECULAR BIOMARKERS OF RESPONSE TO ERIBULIN IN PATIENTS WITH LEIOMYOSARCOMA

Agnieszka Wozniak[1], *Bram Boeckx*[2], *Elodie Modave*[2], *Amy Weaver*[3], *Diether Lambrechts*[2], *Bruce A. Littlefield*[3], *Patrick Schöffski*[1]

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Objective: The recent randomized phase 3 trial Eisai Study 309 evaluated efficacy of eribulin (ERI) compared to dacarbazine (DTIC) in advanced liposarcoma (LPS) and leiomyosarcoma (LMS). Improved overall survival (OS) in ERI-treated patients led to US and EU regulatory approval of ERI for LPS, but not in LMS where DTIC has clinically relevant activity. As part of the translational effort in this trial we have now explored the molecular profile of LMS tumors from North American study sites, in order to identify potential predictive molecular factors for treatment with ERI.

Methods: From 82 archival primary tumor or metastatic LMS samples collected prior to study entry, 78 specimens were available for low-coverage whole genome sequencing. We analyzed copy number alterations (CNAs) and performed whole exome sequencing (WES) for mutational profiling. Forty patients received experimental treatment with ERI, while 38 were treated with DTIC. Treatment response was evaluated using RECIST v1.1; disease control was defined as complete/partial response and stable disease.

Results: Overall 111 focal CNAs were observed in the entire group of LMS, including 55 gains and 56 loses. Gain of 17q12 was the most common CNA (43/78 cases; 55.1%) observed in the entire group analyzed, with 26 samples showing high level amplification. *MYOCD* is a suggested target of 17q12 gains in LMS, encodes myocardin which induces smooth muscle differentiation and promotes cell migration. In the ERI-treated group, gains of 4q26, 20p12.2, 13q13.3, 8q22.2, 8q13.2 and loss of 1q44 had a negative impact on progression-free survival (PFS) ($p<0.05$; log rank test), while loss of 2p12 was a positive prognosticator. Gains of 4q22.1 and losses of 3q14.2, 2q14.1 and 11q25 had a negative impact on OS in ERI-treated patients.

Using WES we detected an average of 266.1 (143-626) nonsynonymous substitutions and 4.7 indels (0-16) per sample, with an average of 11.5 (0-28) variants affecting Cancer Consensus Genes. The most commonly mutated genes in analyzed samples were *TP53* (38%), *MUC16* (31%) and *ATRX* (17%). In ERI-treated patients, the presence of *ATRX* mutations was more frequently observed in patients progressing on ERI (7/20 in patients with PD *vs.* 1/20 in group with disease control; $p=0.0435$). The presence of *ATRX* mutation had a negative impact on both PFS and OS. *TP53* mutations were associated with longer PFS, and these mutations were more frequently observed in patients achieving disease control, although this was not statistically significant (11/20 *vs.* 5/20). *ATRX* and *TP53* mutations were not linked with clinical benefit/response to DTIC.

Conclusion: LMS has a complex genetic background, with multiple CNAs and mutations affecting genes implicated in tumorigenesis. We identified several molecular changes with potential impact on disease control and survival of LMS patients treated with ERI. These observations require further prospective validation.

Poster #074 3458723

GENETIC PROFILE OF GASTROINTESTINAL STROMAL TUMORS (GIST) TREATED IN EORTC 1317 "CABOGIST" PHASE 2 TRIAL

Agnieszka Wozniak[1], *Huiwen Che*[2], *Isabelle Vanden Bempt*[2], *Tatjana Jatsenko*[2], *Laura De Meulemeester*[3], *Ionela Stanciu*[3], *Olivier Mir*[4], *Peter Hohenberger*[5], *Hans Gelderblom*[6], *Raf Sciot*[7], *Joris Vermeesch*[2], *Patrick Schöffski*[1]
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Objective: EORTC 1317 "CaboGIST" trial demonstrated clinically relevant anti-tumor activity of cabozantinib (CABO), a multi-target tyrosine kinase inhibitor, in patients with metastatic GIST who had progressed on imatinib and sunitinib. Using historical tumor material and on-study cell-free DNA (cfDNA) samples, collected during CABO treatment, we performed molecular profiling to correlate molecular results obtained at the cfDNA level with mutations present in archival tumor samples.

Methods: From 50 patients enrolled in the study we were able to collect 43 archival, formalin fixed, paraffin embedded (FFPE) blocks from primary or metastatic tumors. Plasma for cfDNA extraction was collected at study baseline (W0, 47 samples), week 6 (W6, n=44), week 12 (W12, n=37) and at time of progression (PD, n=31), using Streck Cell-free DNA BCT® tubes processed by the participating institutions. Libraries for targeted next-generation sequencing (tNGS) from tumor and cfDNA were prepared using the KAPA HyperPlus Library Preparation Kit (Roche) and sequenced using a custom-made panel of 97 genes and hybrid capture (XGen lockdown probes IDT, Illumina Nextseq 500, 2 x 150 bp paired-end sequencing). Investigated genes included the full exonic sequence of known GIST drivers (*KIT, PDGFRA, BRAF, NF1*, *SDHX*). Three tumor samples without a driver mutation on tNGS were subject to an exploratory gene fusion analysis (Archer FusionPlex CTL panel).

Results: Central tNGS was performed in 37/43 tumor samples. In 31/37 (83.8%) specimens we identified *KIT* mutation, one (2.7%) had *PDGFRA* mutation and two (5.4%) had *NF1* frameshift mutation. In one case without a known driver by tNGS *RBPMS-NTRK3* fusion was revealed by Archer panel. No pathogenic driver mutation was found in only two (5.4%) tumor samples. Additional (likely) pathogenic variants were identified in six samples, affecting *PIK3CA* (2), *CDKN2A* (1), *PIK3R1* (1), *RB1* (1), *ARID1A* (1), and *BRCA2* (1).

The analytical cohort for cfDNA analysis included 157 samples from 48 consenting patients. In 139 samples (88.5%) the quantity and quality of material allowed the library construction and sequencing (39 from W0, 44 from W6, 25 from W12, and 31 collected at PD). Successful sequencing was completed in 136 samples (86.6%). A primary driver mutation was found in 18/39 W0 samples (46.2%), with an allelic frequency (AF) of 0.15 - 31.74%. In additional 8 cases the driver mutation was only identified at a later timepoint, giving a total of 26/48 (54.2%) cases with GIST driver identified on cfDNA level. In 22/26 (84.6%) cases, in which driver mutation detected on cfDNA level, the same mutation was present in the tumor sample. In 14/48 (29.2%) patients no potential driver was identified on cfDNA level, even though such mutation was present in archival tumor DNA. In only 5 samples secondary *KIT* mutations were identified in W0, all affecting *KIT* exon 17 (AF 0.91 - 10.12%). In 4 cases more than one exon 17 mutation was identified at W0.

Conclusion: tNGS of archival tissue confirmed the genetic diversity of GIST. Driver mutations in plasma samples were identified in half of all patients, with a good correlation between mutational results comparing cfDNA and archival tissue samples, suggesting the relevance and some potential advantages of the liquid biopsy approach.

Poster #075 3458771

LONG-TERM OUTCOME OF PATIENTS WITH NONMETASTATIC BONE OSTEOSARCOMA: A CONDITIONAL SURVIVAL ANALYSIS

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Objective: Conditional survival provides a dynamic prediction of prognosis for patients surviving a defined period of time after diagnosis. This study aimed to determine the conditional survival and prognostic factors over time among patients with non-metastatic bone osteosarcoma.

Methods: We reviewed 714 bone osteosarcoma patients treated from 1985 to 2016. Patients with metastatic disease at diagnosis or limited follow up were excluded, resulting in 587 cases for analysis. Clinical and pathological variables were recorded. Predictive variables included age at diagnosis, gender, previous radiation history, tumor site, tumor size, histologic subtype, histologic grade, resection margin, chemotherapy, and radiation therapy. The multivariate Cox proportional hazards regression was used to analyze prognostic factors of conditional overall survival and progression-free survival at baseline and 5 years after diagnosis.

Results: The estimated 5-year conditional overall survival improved from 71.0% (95% CI: 67.5%-75.0%) at baseline to 86.9% (95% CI: 82.6%-90.5%) at 5 years, which means if a patient with non-metastatic bone osteosarcoma survived 5 years, the chance of surviving another 5 years was 86.9%. If the patient was progression-free for 5 years, the 5-year conditional overall survival was even higher, 93.2% (95% CI: 89.5%-96.4%), and the 5-year conditional progression-free survival improved from 57.1% (95% CI: 53.3%-61.0%) at baseline to 91.2% (95% CI: 87.5%-94.6%) at 5 years. Prognostic factors for mortality and disease progression change as survival time increases. At baseline, age ($p<0.001$ and $p=0.003$), histology subtype ($p<0.001$ and $p=0.001$), grade ($p<0.001$ and $p<0.001$), tumor size ($p=0.003$ and $p=0.002$), resection margin ($p<0.001$ and $p<0.001$) and chemotherapy ($p=0.001$ and $p=0.001$) were predictive of both overall survival and progression-free survival. However, only age ($p<0.001$) and histology subtype ($p=0.015$) remained significant for mortality and histology ($p=0.002$) for disease progression at 5 years.

Conclusion: The survival probability of osteosarcoma improves as survival time increases. Estimates of conditional survival can provide useful information for individualized surveillance strategies, risk evaluation, patient counseling, and making clinical decisions.

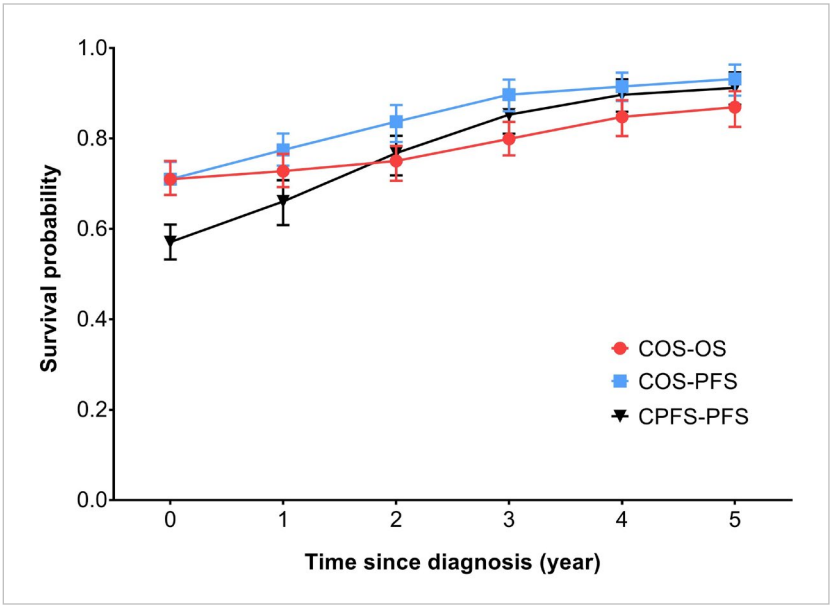

IMAGE CAPTION:
Five-year conditional survival probabilities: red, five-year conditional overall survival (COS) probability as a function of overall survived period since diagnosis (COS-OS); blue, five-year conditional overall survival (COS) probability as a function of progression-free period since diagnosis (COS-PFS); black, five-year conditional progression-free survival (CPFS) probability as a function of progression-free period since diagnosis (CPFS-PFS). Error bars denote 95% CIs.

Poster #076 3458918

EVALUATION OF PROGNOSTIC NOMOGRAMS FOR OUTCOMES AFTER RESECTION OF PRIMARY RETROPERITONEAL SARCOMA

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Objective: By incorporating histology-specific variables, several nomograms have been developed for patients undergoing resection of retroperitoneal sarcoma to enhance prognostic modeling beyond the limitations of American Joint Committee on Cancer (AJCC) staging. Two of the most widely employed nomograms include the Sarculator nomogram, which predicts 7-year disease-free (DFS) and overall survival (OS), and the Memorial Sloan Kettering (MSK) sarcoma nomogram, which predicts 4-year, 8-year, and 12-year disease-specific survival (DSS). The aim of the present study was to validate the applicability of the Sarculator and MSK nomograms among a modern cohort of patients undergoing resection of primary retroperitoneal sarcoma at a high-volume regional cancer center.

Methods: Patients who underwent definitive resection of primary retroperitoneal sarcoma between 2004-2017 at a single, high-volume cancer institute were identified. Retrospective review of clinical and operative records was conducted and clinicopathologic variables were analyzed. Patients with missing data related to nomogram variables were excluded from analysis.

Predicted 7-year DFS and OS calculated from the Sarculator nomogram were compared in calibration plots to observed survival outcomes as calculated by Kaplan-Meier analysis. Patients were analyzed in quintiles stratified by nomogram-predicted survival probabilities. Similarly, predicted 4-year, 8-year, and 12-year disease-specific survival (DSS) calculated from the MSK nomogram were compared in calibration plots to observed DSS outcomes. Discriminative ability of the nomograms was quantified by the Harrell C concordance index.

Results: 103 patients (57% male), with a median age of 63, who underwent resection of primary retroperitoneal sarcoma were identified (Table). The most common histologic subtypes included dedifferentiated liposarcoma (38%), leiomyosarcoma (29%), and well-differentiated liposarcoma (15%). Median tumor size was 17.0 cm (IQR, 10.0 – 30.0cm) and tumor grade was classified by FNCLCC criteria: Grade 1 (24%), Grade 2 (38%), Grade 3 (38%). Median follow-up time for all patients was 51.8 months. Median DFS was 60.6 months, with 7-year DFS of 45%. Median OS was 96.0 months, with 7-year OS of 54%.

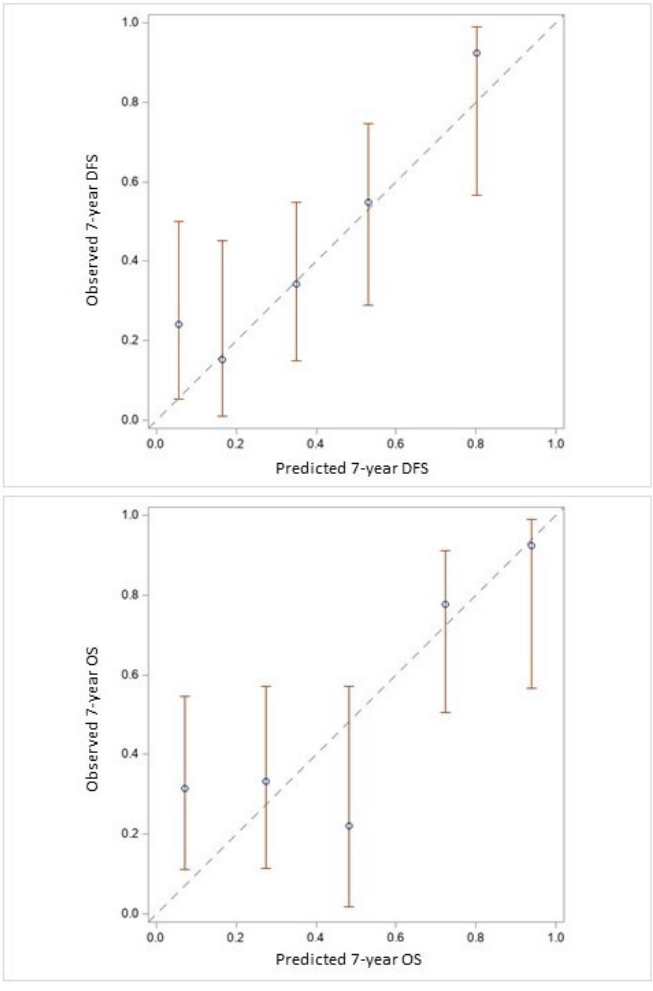
The concordance indices for 7-year DFS and 7-year OS using the Sarculator nomogram were 0.71 and 0.75, respectively. Calibration plots demonstrated that the Sarculator nomogram had good predictability for 7-year survival outcomes within our patient population (Figure). The concordance indices for 4-year, 8-year, and 12-year DSS using the MSK nomogram were 0.75, 0.74, and 0.74, respectively, with plots demonstrating similarly good calibration ability of the nomogram.

Conclusion: Among patients who underwent resection of primary retroperitoneal sarcoma, both the Sarculator and MSK nomograms demonstrated good calibration and discriminatory ability for prognostication of survival outcomes. Further evaluation of the efficacy of these nomograms within larger patient populations and as stratification tools to identify high-risk patients subsets within clinical trial study cohorts is warranted.

Clinicopathologic variables of patients undergoing resection of primary retroperitoneal sarcoma (n=103)

Variable	Median (IQR) or N (%)
Age, years	63 (IQR, 51 - 72)
Tumor size, cm	17.0 (IQR, 10.0 - 30.0)
FNCLCC Grade 1 2 3	 25 (24%) 39 (38%) 39 (38%)
Histology LMS DDLPS WDLPS MPNST UPS SFT Other	 30 (29%) 39 (38%) 16 (15%) 4 (4%) 4 (4%) 4 (4%) 6 (6%)
Multifocality	18 (18%)
Completeness of resection R0/R1 R2	 95 (92%) 8 (8%)

IQR, interquartile range; FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; LMS, leiomyosarcoma; DDLPS, dedifferentiated liposarcoma; WDLPS, well-differentiated liposarcoma; MPNST, malignant peripheral nerve sheath tumor; UPS, undifferentiated pleomorphic sarcoma; SFT, solitary fibrous tumor



Calibration plots of observed 7-year disease-free survival (DFS) and overall survival (OS) versus predicted 7-year DFS and OS probability using the Sarculator nomogram

Poster #077 3459835

DEVELOPMENT OF RHABDOMYOSARCOMA SPECIFIC SEQUENCING ASSAY

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Objective: Circulating tumor DNA (ctDNA) is a promising approach to monitoring treatment responses in cancer but has not yet been systematically applied to pediatric sarcomas. Detecting ctDNA requires identification of somatic variants. In rhabdomyosarcoma (RMS), characteristic variants include translocations, single nucleotide variants (SNVs) in recurrently mutated genes, copy number alterations (CNAs), or a combination of somatic events. Accurate tumor profiling which can robustly detect each type of alteration can facilitate the selection of the most sensitive and relevant ctDNA assay for each patient with RMS. For example, digital droplet PCR (ddPCR) can identify ctDNA using patient-specific primers to detect translocations or variant-specific probes to detect SNVs. Genomic alterations can also be detected by deep sequencing of a targeted panel of genes. In cases without recurrent translocations or mutated genes, CNAs can be detected and leveraged to estimate ctDNA content using shallow whole-genome sequencing. We developed an RMS-specific hybrid capture sequencing assay to profile tumors collected from patients enrolled on the Children's Oncology Group RMS study, ARST1431. This assay will be used to profile tumor samples which will allow appropriate selection of ctDNA strategies for profiling serial plasma samples collected on this trial.

Methods: An RMS-specific custom next generation sequencing assay was created to detect fusions known to be found in rhabdomyosarcoma, including *PAX3/PAX7-FOXO1* which define alveolar RMS and rare fusions involving *NCOA2*, *VGLL2*, *CITED2*, and *NCOA1* which are commonly associated with spindle-type RMS. The assay was also designed to detect SNVs in genes commonly mutated in embryonal RMS, including *PIK3CA, KRAS, PTEN, ARID1A, BCOR, FGFR4, CTNNB1, NRAS*, and a rare but recurrent variant in *MYOD1*. To test this custom assay, FFPE tissue was obtained from patients enrolled on COG trials ARST0531 and ARST1431 with *FOXO1* fusion positive and negative RMS, as well as from patients at Dana-Farber Cancer Institute with histologic features consistent with spindle or sclerosing soft-tissue sarcomas (ssSTS). DNA was sequenced and analyzed using publicy available fusion and mutation detection algorithms. DNA was extracted from two unstained slides of tumor for COG specimens and 5-10 slides for ssSTS samples.

Results: We sequenced 47 RMS samples with FISH-confirmed rearrangements of *FOXO1* (aRMS), 31 samples defined histologically as embryonal RMS (eRMS), and 12 samples with histological characteristics of ssSTS. Of the aRMS samples, 30 *FOXO1* translocations were identified by Rhabdo-seq, including 3 *PAX7-FOXO1* and 27 *PAX3-FOXO1* translocations. Of the eRMS samples, no *FOXO1* fusions were found, as expected, however two rare fusions, *PAX3-NCOA2* and *SRF-NCOA2*, were identified. Oncogenic mutations in recurrently mutated genes were also identified in the eRMS cohort, including mutations in *FGFR4*, *PIK3CA*, and *CTNNB1*. In the ssSTS cohort, fusions were found in 2 patients (*HEY1-NCOA2*, and *VGLL2-NCOA2*) and SNVs were identified in 3 patients (*NRAS*, *FGFR4*, and *MYOD1*). While we currently detect 30 of 47 known FOXO1 fusions, assay-specific optimization of the computational algorithms is ongoing and expected to further improve sensitivity.

Conclusion: This newly designed RMS-specific assay can detect prognostically valuable fusions and mutations in pediatric patients with RMS. Assay validation was performed with minimal tissue input, fulfilling a required performance characteristic for use in a multi-institutional study where access to tissue samples is frequently limited. We expect this assay will support selection of the most appropriate ctDNA assays for blood samples collected from patiets enrolled on the COG study ARST1431. Efforts are now ongoing to determine whether this assay can also be used to directly detect and quantify ctDNA in patients with RMS.

Poster #078 3459966

THE PROGNOSTIC IMPORTANCE OF PATHOLOGIC FRACTURE IN LIMB SALVAGE SURGERY FOR OSTEOSARCOMA: A SINGLE-INSTITUTION REVIEW OF 304 PATIENTS

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Objective: Historically, the presence of a pathologic fracture (PF) in patients with osteosarcoma has been considered a poor prognostic factor and an indication for amputation. The purpose of this study was to utilize a large database of cemented stem endoprosthetic reconstructions with long-term follow-up to determine whether the presence of a PF impacts prognosis in patients who undergo limb salvage surgery for osteosarcoma. In addition, the authors sought to determine whether implant survival is affected by the presence of a PF.

Methods: 304 consecutive patients who underwent limb salvage surgery with cemented stem endoprosthetic reconstruction for osteosarcoma of the extremity between December 1980 and December 2019 were retrospectively reviewed. The average follow-up of surviving patients was 13.0 years (range: 0.2 – 37.7yrs). All follow-up was performed at a single institution. Patients who presented with a PF or sustained one during preoperative chemotherapy were compared to patients without a PF with regard to demographic, oncologic, procedural, and outcome data. Implant failure was defined by major revision surgery or amputation.

Results: 17 patients (5.6%) had a PF prior to limb salvage surgery. PF patients were similar to patients without fracture with regard to average age (24.7 vs 22.4 yrs; p=0.52), sex (52.9% vs 57.1% male; p=0.73), disease stage (11.8%/76.5%/11.8% vs 8.3%/80.2%/11.5% stage I/II/III; p=0.88), and average tumor necrosis (74.7% vs 69.5%; p=0.46). 29.4% of patients with PF died of disease compared to 31.0% of patients without PF (p=0.89). Disease-specific patient survival was similar at 25 years between patients with and without a PF (66.8% vs 63.0%; p=0.80) (Figure 1). 35.2% of patients with a PF developed distant metastases compared with 38.3% of patients without a PF p=0.80). The incidence of local recurrence was higher in patients with a PF compared to patients without a PF (17.6% vs 9.4%; p=0.27). For patients with a PF, survival to local recurrence was 87.4% and 80.7% at 1 and 3 years, respectively, compared to 94.2% and 89.7% for patients without a PF (p=0.25) (Figure 2). In total, 22 patients without PF required amputation (7.7%), 3 of which were for infection and the remaining 19 of which were for tumor progression. No patients with PF went on to amputation. Overall survival of limb salvage was 90.1% at 30 years. There was no significant difference in survival of limb salvage between patients with and without PF (100% vs 89.6% at 25 years; p=0.55) (Figure 3). 3 implants (17.6%) failed in the PF group and 72 implants (25.1%) failed in patients without PF (p=0.77). Overall implant survival was 26.0% at 30 years, and did not differ significantly between patients with and without PF (52.3% vs 24.8%, p=0.40).

Conclusion: The presence of a pathologic fracture in patients who undergo limb salvage surgery for osteosarcoma did not significantly impact patient or implant survival, and was not associated with an increased risk of distant metastasis. Limb salvage surgery can be performed in select patients with pathologic fracture through an osteosarcoma with excellent long-term survival. However, the risk of local recurrence may be higher in patients with a pathologic fracture, which should be taken into account when considering limb salvage surgery.

Figure 1: Disease-specific survival following limb salvage surgery for osteosarcoma was not significantly different between patients with and without pathologic fracture (p=0.80)

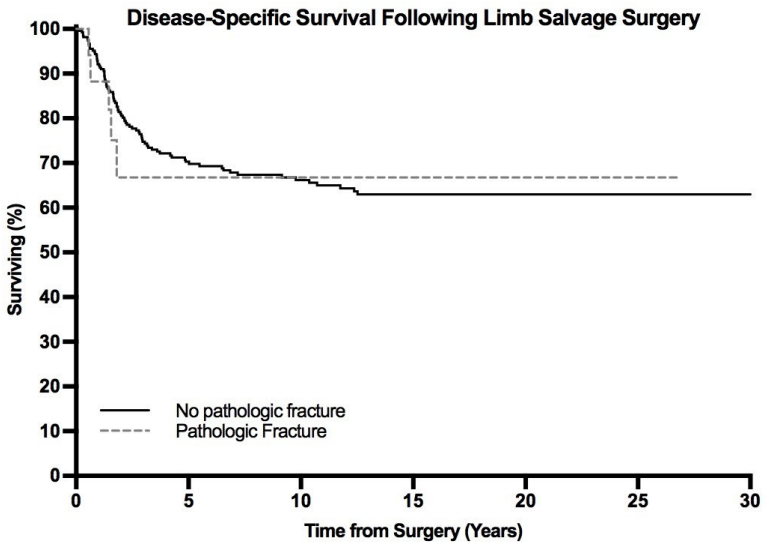


Figure 2: Survival to local recurrence following limb salvage surgery for osteosarcoma was lower in patients with a pathologic fracture compared to patients without a pathologic fracture (p=0.25).

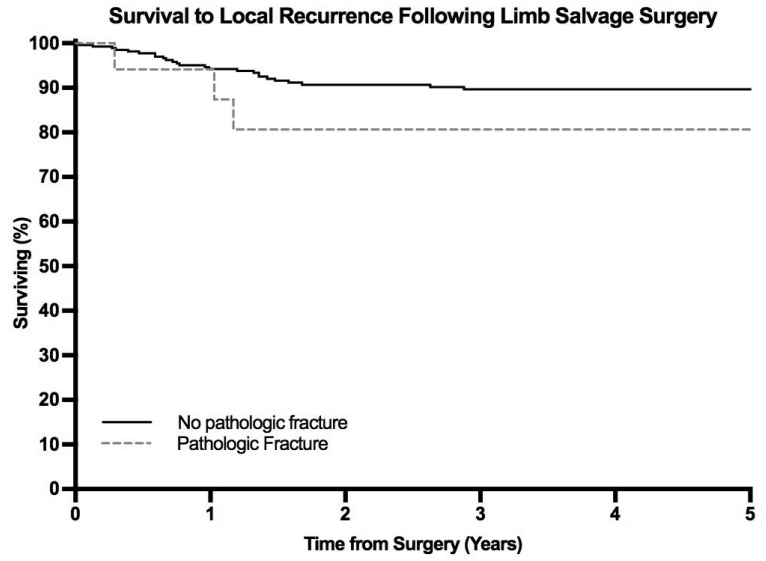
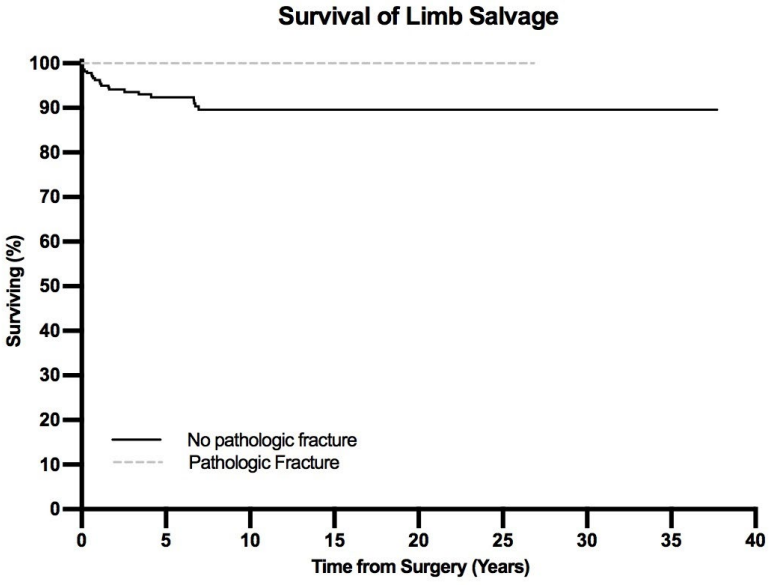


Figure 3: Survival of limb salvage did not differ significantly between patients with and without pathologic fracture following surgical treatment for osteosarcoma (p=0.55).



Poster #079 3459977

SARCOMA IN YOUNG AGE – AN OVERVIEW OF CLINICAL, PATHOLOGICAL AND MOLECULAR FINDINGS IN A LARGE SINGLE CENTER COHORT

Samuele Renzi[1], *Noelle Cullinan*[1], *Sarah Cohen-Gogo*[1], *Karin Langenberg-Ververgaert*[1], *Orli Michaeli*[1], *Jalila Alkendi*[1], *Anne L. Ryan*[1], *Bailey Gallinger*[2], *Katrina M. Ingley*[1], *Sevan Hopyan*[3], *Rose Chami*[4], *Abha A. Gupta*[1]
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Objective: Soft tissue sarcomas (STS) are rare and account for approximately 7% of all pediatric malignancies. The disease spectrum in pediatric sarcoma (sarcoma subtypes, sites involved, disease responsiveness, outcome) differs substantially from that seen in adults. Five-year survival outcomes in young children vary widely, depending on underlying histological diagnosis, extent of disease and therapies administered. Infantile fibrosarcoma (IFS) classically is associated with the best outcome, whereas other subtypes such as malignant rhabdoid tumors (MRT) fare exceptionally poorly. Despite significant advances in the field of molecular diagnostics, literature regarding biological and molecular findings in STS occurring in young age is sparse and management of sarcoma in infants and young children remains challenging. This study was envisioned to describe the clinical, pathological and molecular characteristics of a large cohort of young patients with STS in a tertiary-care pediatric oncology center.

Methods: Following institutional research ethics board approval, this retrospective single center descriptive study collated and analyzed the clinical, pathological and molecular features of children with a diagnosis of STS at age <2 years, who were diagnosed and/or treated at The Hospital for Sick Children (January 1st 2000 - December 31st 2017). Clinical data were retrieved from electronic health records and archival pathological material was reviewed, with additional molecular techniques applied where indicated.

Results: Thirty patients (17 females; 57%) had a diagnosis of STS, with a median age at diagnosis of 6 months (range, 0-23 months). STS subtypes included IFS (n=14, 46.7%), MRT (n=4, 13.3%), undifferentiated sarcoma not otherwise specified (n=3, 10%), pleuropulmonary blastoma (n=2, 6.7%), clear cell sarcoma of kidney (n=2, 6.7%), and one (3.3%) each of dermatofibrosarcoma protuberans, Ewing sarcoma, fibrosarcoma (adult type), embryonal rhabdomyosarcoma and undifferentiated round cell sarcoma. The predominant clinical presentation was a swelling/mass (n=24; 80%) followed by respiratory symptoms (n=5; 16.7%). Disease extent was localized (n=21; 70%), locoregional (n=6; 20%) or metastatic (n=3; 10%). 28/30 (93%) patients had a surgical resection performed (complete: n=17, 57%; R1: n=9, 30%; R2: n=4, 13%). Neoadjuvant and/or adjuvant chemotherapy was administered in 27 (90%) patients. Three patients (10%) received targeted therapy with an oral tyrosine kinase inhibitor. Five patients (16.7%) received adjuvant radiation, with curative intent in 4/5 patients.
At last follow-up (median 3.7 years), 24 patients (80%) were alive without evidence of disease, including all patients with IFS. Six (20%) patients succumbed to disease (MRT: n=4; undifferentiated sarcoma: n= 2).
Molecular characterization of the tumor was available in 28/30 (93%) patients and was supportive of the pathological diagnosis in all cases. 3/4 cases of undifferentiated sarcoma could not be further clarified despite extensive molecular studies. A pathogenic germline variant in a cancer predisposing gene was confirmed in 3/11 patients who underwent genetic evaluation (*SMARCB1*: n=1; *DICER1*: n=1; *NF1*: n=1).

Conclusion: This retrospective descriptive study confirms that the prognosis of young children (<2 years) with STS is largely dependent on tumor subtype. We recommend molecular characterization of all tumors and careful consideration of the need for genetic evaluation for an underlying cancer predisposition syndrome in all patients. Efforts must continue to focus on therapy de-escalation in tumors with good prognosis, considering potentially targetable molecular findings, such as NTRK fusions in IFS. Conversely, it is crucial to appropriately identify patients who require therapy intensification for disease subtypes (*e.g.* MRT, undifferentiated sarcomas) that have poor outcomes despite multimodal therapy.

Poster #080 3460220

THE UTILITY OF FDG PET-CT SCAN IN OFF-TREATMENT SURVEILLANCE OF PEDIATRIC BONE TUMORS

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Background: The commonest bone tumors in children and adolescents are osteogenic sarcoma (OS) and Ewing sarcoma (ES). Following completion of chemotherapy (C), surveillance imaging studies are performed to identify relapse. Since 2006, we progressively incorporated fluorodeoxyglucose positron emission tomography (PET) scanning into our surveillance (S) strategies.

Objective: To report our use of PET scan, its utility in identifying recurrences, and any evidence that PET may identify recurrences not detected using other modalities.

Methods: We analyzed patients treated for OS and ES in the PET era. Patients were included in the analysis if they completed treatment in clinical remission and underwent S at our institution. From the time of completion of C, we quantified the number of surveillance PET (S-PET) scans. In patients known to have had a relapse, PET scan and other imaging/clinical reports were reviewed to determine how that relapse was identified.

Results: Between 2006 and 2020 there were 63 and 63 patients respectively with OS and ES. 93 patients completed treatment in remission, and underwent surveillance within our institution. 13 did not undergo S-PET. 80 patients underwent S-PET, having 1-14 S-PET (median 5). 430 S-PETs were performed. 63/80 (79%) patients had no recurrence. 17/80 (21%) experienced disease recurrence after 1-10 S-PET (median 2). PET scan was positive at recurrence in 15/17 relapse cases. In 2/17 S-PET was not scheduled at time of relapse: 1 patient presented between scans with bone pain, and 1 had relapse detected during prosthesis revision. Of 430 total S-PET, 15 demonstrated relapse (3.5%). In 9/15 of these patients, relapse was also detected on other surveillance imaging. In 6/15 cases PET was the only modality demonstrating the relapse (1.4% of S-PET): 4 had bony recurrence, 1 had primary site recurrence, and 1 had a lung nodule and wasn't undergoing other scans at the time. 10/17 patients experienced relapse that included lung recurrence and had S-PET at the time: the pulmonary recurrence was seen in all 10 either on the low-energy CT which is part of the S-PET, or by FDG uptake.

Conclusion: Relapse occurred in 21% of patients during surveillance. S-PET was positive in 15/17 relapses, including 15/15 having scheduled S-PET at time of relapse, and not performed in 2/17. The low energy computed tomography images in S-PET detected all pulmonary relapses. S-PET identified 6 relapses which would not have been otherwise identified. 96.5% of S-PET were negative. These data will aid optimization of practice so as to minimize radiation exposure and identify relapse.

Poster #081 3460229

NEUTROPHIL-LYMPHOCYTE AND PLATELET-LYMPHOCYTE RATIOS AS ROBUST PROGNOSTIC MARKERS IN SARCOMAS - A POPULATION-BASED ANAYLSIS OF 3746 SARCOMA PATIENTS FROM HONG KONG

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Objective: Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been shown to be prognostic in various cancers. Prior reports of this in sarcomas have predominantly been made through smaller cohorts from single institutions. We investigated the prognostic implications of these indices in patients with soft-tissue (STS) and bone sarcomas using a large population-based database.

Methods: A population-based retrospective database was assembled to extract pts with sarcoma, as defined as ICD-9-CM codes of bone (170.x) or/and soft tissue (171.x) who have attended clinics or hospitals of the Hong Kong Hospital Authority between Jan 2004 and Mar 2018. Eligible patients (pts) with index presentation of bone sarcoma or/and STS on or after Jan 2005 were analysed to allow 1-year window. The most recent documented lymphocyte, neutrophil, and platelet counts from the index date of sarcoma diagnosis were retrieved, and the neutrophil-lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) were correlated with survival. Abnormal (abn) NLR and abn PLR are defined as NLR≥2.5 and PLR≥182 respectively. Restricted cubic spline plots were used to explore the shape of association between baseline NLR and PLR and all-cause mortality, fitting a restricted cubic spline function with four knots (5th, 35th, 65th, and 95th centiles).

Results: Of 3746 pts identified, 3358 pts satisfied eligibility: bone n=661, STS n=2576, both n=121. NLR and PLR is available for 89.93% (n=3020) of eligible pts, amongst which 65.9% (n=1989) had abn NLR while 47.6% (n=1438) had abn PLR., Abn NLR and abn PLR are each associated with higher all-cause mortality (abn NLR: HR 1.698, p<0.001, 95% CI 1.424-2.025; abn PLR: HR 1.346, p<0.001, 95%CI 1.164-1.555) and cancer-related mortality (abn NLR: HR 1.648, p<0.001, 95% CI 1.341-2.024; abn PLR: HR 1.430, p<0.001, 95% CI 1.205-1.697).

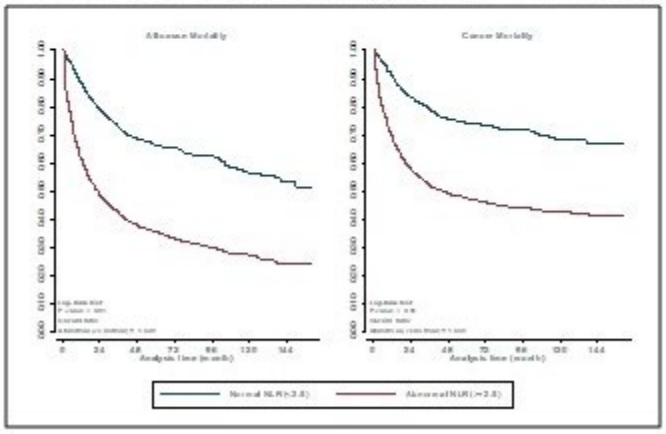
Conclusion: This is the largest assembled population-based sarcoma cohort in Asia. We show that NLR and PLR are robust prognostic factors, and abn NLR and PLR have negative effects on survival. More importantly, the relationship between NLR and PLR and mortality is shown to be non-linear.

Kaplan-Meier Curves of All-cause & Cancer-related Mortality for Abnormal vs. Normal NLR and Abnormal vs. Normal PLR

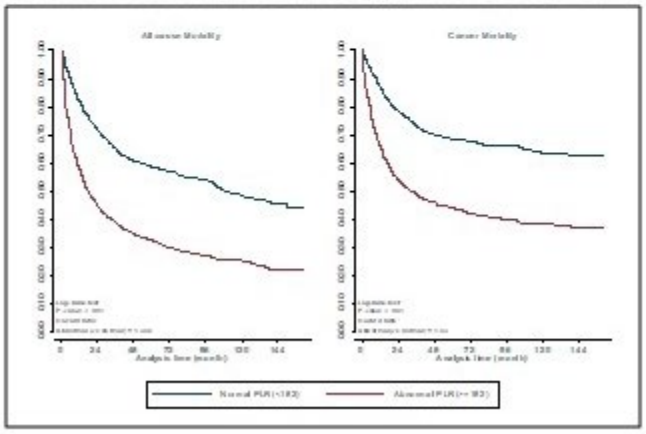
Results

	Abnormal NLR (NLR≥2.5)	Abnormal PLR (PLR≥192)
HR for all cause mortality	1.698 (95% CI 1.424-2.025)	1.346 (95% CI 1.164-1.555)
HR for cancer-related mortality	1.648 (95% CI 1.341-2.024)	1.430 (95% CI 1.205-1.697)

All cause & cancer-related mortality (normal vs abnormal **NLR**)

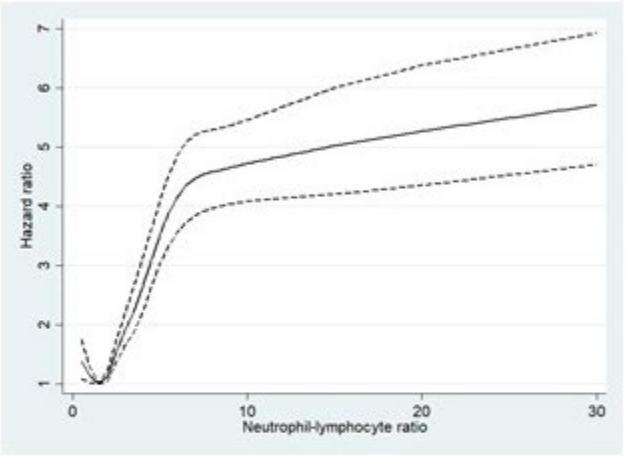


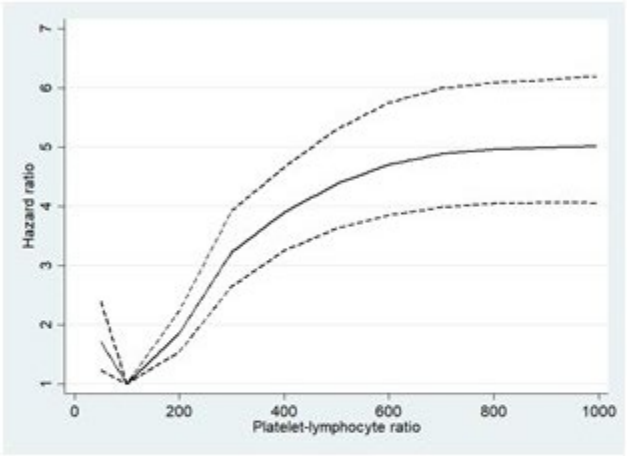
All cause & cancer-related mortality (normal vs abnormal **PLR**)



Restricted cubic spline plots indicating non-linear relationship of Hazard Ratio of Mortality in relation to NLR and PLR

Results





restricted cubic spline plots

Poster #082 3460268

AGE RELATED DIFFERENCES OF ONCOLOGICAL OUTCOMES IN PRIMARY EXTREMITY SOFT TISSUE SARCOMA: A MULTISTATE MODEL INCLUDING 6260 PATIENTS

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Objective: In the last decade, there has been an increase in awareness of differences in therapeutic outcomes and biology of extremity soft tissue sarcoma (eSTS) across the age spectrum. However, no studies extensively compared the adolescents and young adults (AYA, 18-39 years), middle-aged (40-69 years), and elderly (≥70 years) population with primary high-grade eSTS. This study aimed to determine whether the known effect of age on overall survival (OS) and disease progression can be explained by differences in tumor characteristics and treatment protocol among the AYA, middle-aged, and elderly population in primary high-grade eSTS patients treated with curative intent.

Methods: In this retrospective multicenter study, inclusion criteria were patients with primary high-grade eSTS of 18 years and older, surgically treated with curative intent between 2000 and 2016. Cox proportional hazard models and a multistate model were used to determine the association of age on OS and disease progression.

Results: A total of 6260 patients were included in this study. The population was categorized into three age groups: the AYA population aged 18-39 years (n = 841, 13.4%), the middle-aged population aged 40-69 years (n = 3,217; 51.4%) and the elderly population aged ≥70 years (n = 2,202; 35.2%). AYA presented more often after "whoops" surgery or for re-resection due to residual disease, and with more deep-seated tumors. Elderly patients presented more often with grade III and larger (≥10cm) tumors. Age was significantly associated with OS in the univariate model (HR middle-aged: 1.47 (95%CI 1.26-1.72), HR elderly: 3.36 (95%CI 2.88-3.93), AYA as reference). After adjustment for the presentation and treatment variables the association between age and OS decreased, but remained significant (HR middle-aged: 1.41 (95%CI 1.20-1.66), HR elderly: 2.98 (95%CI 2.50-3.54), AYA as reference). Also, age demonstrated a significant effect on the cause-specific hazard of LR and DM. The difference in the cause-specific hazard of LR among the age groups could partially be explained by the imbalance in tumor and treatment characteristics. The imbalance in tumor and treatment characteristics does not seem to explain the difference in the cause-specific hazard of DM among the age groups.

Conclusion: In this large multicenter study, we observed a significant decrease in OS and increase in LR and DM rate with increasing age. This can only partially be explained by differences in tumor characteristics and treatment strategies, suggesting that eSTS may have a more aggressive tumor behavior in elderly patients compared with their younger counterparts, which may coincide with a weaker tumor-specific immune response in elderly patients.

Table 1. HRs of age for overall survival and all transitions in the multivariable multistate model

Age	OS HR (95% CI)	TRANS 1 ANED → LR HR (95% CI)	TRANS 2 ANED → DM HR (95% CI)	TRANS 3 ANED → Death HR (95% CI)	TRANS 4 LR → DM HR (95% CI)	TRANS 5 LR → Death HR (95% CI)	TRANS 6 DM → Death HR (95% CI)
- AYA	1	1	1	1[$]	1	1	1
- Middle-aged	1.41 (1.20-1.66)	1.40 (1.03-1.91)	1.22 (1.05-1.41)		1.09 (0.651-1.82)	1.60 (0.585-4.39)	1.14 (0.952-1.36)
- Elderly	2.98 (2.50-3.54)	2.04 (1.47-2.84)	1.25 (1.05-1.48)	5.89 (4.87-7.13)	0.679 (0.381-1.21)	5.48 (2.02-14.7)	1.91 (1.57-2.34)

Adjusted for histology, grade, size, depth and tumor site, surgical margin, (neo)adjuvant radiotherapy and (neo)adjuvant chemotherapy. For transition 3 (ANED→Death), we grouped the AYA and middle-aged population due to the relatively small number of patients in this transition for these age groups. For transition 5 (LR→Death), we only adjusted for tumor characteristics due to the relatively small number of patients in this transition. Supplement 2 includes the full multistate model including het HRs of the adjusted variables.
[$] For transition 3 the AYA and Middle-aged group were combined in one group
OS: Overall survival, ANED: Alive, no evidence of disease, LR: Local recurrence, DM: Distant metastasis, HR: Hazard ratio, AYA: Adolescents and young adults

Poster #083 3460427

ANALYSIS OF TUMOR INFILTRATING NK AND T CELLS HIGHLIGHTS IL-15 STIMULATION AND TIGIT BLOCKADE AS A COMBINATION IMMUNOTHERAPY STRATEGY FOR SOFT TISSUE SARCOMAS

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Objective: Although tumor infiltrating lymphocytes (TILs) have been shown to be prognostic factors for outcome and response to immunotherapy in multiple cancer types, including soft tissue sarcomas (STS), the benefits of immunotherapy in STS have been limited, and novel approaches are needed. In this study, we sought to characterize the phenotype and function of tumor infiltrating natural killer (NK) and T cells in STS patients and to evaluate clinically relevant strategies to augment TIL function.

Methods: Using prospectively collected blood and tumor tissue from patients undergoing surgery, archived specimens, and TCGA data, we evaluated the phenotype and functions of peripheral and intratumoral NK and T cells as predictors of outcome in STS. We also analyzed the peripheral blood of pet dogs with naturally occurring osteosarcoma receiving inhaled IL-15 on a clinical trial to determine in vivo effects of IL-15 on NK and T cell activation as well as TIGIT upregulation. Finally, we stimulated STS patient PBMCs and TILs ex vivo with IL-15 and a novel human anti-TIGIT antibody to assess the impact of the combination on NK and T cell cytotoxic function.

Results: Among 21 patients with locally advanced STS, blood NK and T cells demonstrated limited expression of activation markers and variable expression of inhibitory markers. In contrast, intra-tumoral NK and T cells showed significantly greater expression of activation markers (CD69) and exhaustion markers (TIGIT). Importantly, ex vivo stimulation of circulating NK and T cells with IL-15 simultaneously increased both activation and exhaustion marker expression. IHC analysis of a retrospective STS cohort and TCGA STS gene expression data each confirmed the association of TILs with significantly improved oncologic. Dogs with metastatic osteosarcoma receiving inhaled IL-15 exhibited similar changes in blood NK and T cells with increased expression of granzyme B with simultaneous upregulation of TIGIT. The combination of ex vivo stimulation of human blood and tumor NK and T cells with IL-15 and TIGIT blockade led to heightened cytotoxic function in killing assays against STS targets.

Conclusion: TILs are associated with improved survival in STS, and intra-tumoral NK and T cells show features of both increased activation and increased exhaustion. Tumor infiltrating NK and T cells' response to IL-15 stimulation is notable for further upregulation of TIGIT. Overall, our data provide support for the combination of IL-15 and TIGIT blockade as a promising clinical strategy in STS.

Poster #084 3460650

MANAGEMENT AND OUTCOMES OF CIC-REARRANGED SARCOMA; AN AUSTRALIAN MULTI-CENTRE REVIEW

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Objective: CIC-rearranged sarcoma is a rare molecularly distinct subtype of undifferentiated high grade round cell sarcoma often presenting in adults of young age (age 25-35) (WHO Classification of Tumours, Soft Tissue and Bone Tumours, 5thedition; CIC-rearranged sarcoma). Understanding of their natural history, clinical behaviour and treatment outcomes is limited. CIC-rearranged tumours are commonly treated with Ewing sarcoma protocols but with poorer treatment responses and outcomes. We aimed to further characterise the clinical features and outcomes of the CIC-rearranged sarcoma.

Methods: Retrospective study of patients with CIC-rearranged sarcoma confirmed on fluorescence in-situ hybridisation (FISH). Clinical presentations, treatment details, responses and outcomes were reviewed.

Results: Ten cases were identified across three sites in Australia between 2014-2019. Median age at diagnosis was 30 years (range 21-56). Six (60%) patients were male. Median follow up is 29.9 months (range 10.8 to 32.4). Primary sites included soft tissue (thigh, gluteus, psoas, trapezius, supraclavicular), bone (pelvis), and visceral (para-testicular, pleural). At diagnosis, six patients (60%) had localised disease and four patients had advanced (metastatic or unresectable [pleura, n=1]). Metastatic disease sites included lung, liver, bone, nodal and brain.

WT-1 immunohistochemistry was positive in seven of the ten cases (not available for three cases). EWSR1 FISH was tested for in seven patients and was negative in all. DUX4 was the CIC-rearrangement partner in three patients. The rearrangement partner was not identified or available for seven patients. Molecular profiling was performed in three patients; no actionable variants were identified and tumour mutational burden was reported as low for three patients.

Of the six patients with localised disease, five underwent surgery, all with R0 resections. Four patients received chemotherapy (VAC/IE [n=2], VDC/IE [n=1], VIDE then switch to VDCE after 2 cycles due to recurrent ifosfamide encephalopathy [n=1]). Four patients received adjuvant radiotherapy to the primary site (median dose 55Gy in 30 fractions). Three of six patients with localised disease developed metastases with a median time to progression of 10 months (range 8-13m). All three are deceased. Of these patients, the first had chemotherapy, radiotherapy and surgery, the second had surgery and radiotherapy and the third patient received chemotherapy, with neo-adjuvant intent, though developed local progression on treatment for which they received palliative radiotherapy. Rapid development of metastatic disease followed.

Of four patients with advanced disease at diagnosis, 3 underwent resection of the primary lesion, 4 received systemic therapies, and 3 received radiotherapy. Systemic treatments included chemotherapy (VDC/IE, VID, VAC, AC, doxorubicin, gemcitabine and docetaxel (n=1), irinotecan and temozolamide (n=1), pembrolizumab (n=1). Median time to progression on systemic treatment (n=8 regimens) was 1.9 (range 0.7-4.1) months. Best response was partial in all except one sustained complete response of oligometastatic disease to seven cycles of VDC/IE chemotherapy. Complete response is ongoing, off treatment, 10 months from commencement. three of these four patients are deceased, including progressive disease and death occurring after 1 cycle in a patient who received pembrolizumab.

Overall survival is shown in the table.Data will be updated, including additional cases, at the meeting.

Conclusion: In this series, CIC-rearranged tumours presented in young adults and had a high incidence of presenting with, or developing, metastatic disease. Durable chemotherapy responses occurred infrequently and prognosis is poor with a median overall survival of 16 months. Targetable molecular variants are infrequent.

Overall survival of patients with CIC-rearranged Sarcoma

-	Overall cohort (n=10)	Localised disease at diagnosis (n=6)	Metastatic disease at diagnosis (n=4)
Median (IQR) in months	16 (IQR: 9.6 to -)	28.9 (IQR: 15.8 to -)	9.6 (IQR: 7.5 to 16.3)
1-year survival (%)	70% (95% CI: 33, 89)	83% (95% CI: 27, 97)	50% (95% CI: 6, 84)
2-year survival (%)	42% (95% CI: 11, 71)	63% (95% CI: 14, 89)	-

IQR: Interquartile range, CI: confidence Interval.

Poster #085 3460865

IDENTIFICATION OF NOVEL THERAPEUTIC TARGETS FOR METASTATIC OSTEOSARCOMA

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Objective: Osteosarcoma (OS) is the most common primary bone malignancy, predominantly affecting children and adolescents. Lung metastasis (LM) portends a poor prognosis, with survival rates ranging from 15-30%. OS mortality has remained unchanged for the past 30 years due to a poor understanding of the mechanisms of metastasis. Our objective is to identify OS-specific gene alterations with a focus on those that drive LM in a genetic comparison of primary and metastatic human tissue.

Methods: Patients with OS treated surgically at our institution between 2000 and 2017 were identified and archived samples from primary and metastatic tumors were obtained. Chart review was performed to obtain the clinical characteristics of each patient. Forty-two samples from 32 patients passed quality control and were included in the transcriptomic analyses, including 13 samples from primary tumors in patients that never developed LM, 15 samples from primary tumors in patients that did develop LM, 10 LM samples, and four recurrences. RNA was extracted from FFPE samples and total RNA library preparation was performed, followed by sequencing on an Illumina NextSeq 500. Greater than 50 million, 150 bp paired-end reads were generated for each sequenced tumor. RNA transcript abundance was quantified and normalized from paired-end FASTQ files and then mapped to hg38 build via Salmon algorithm. Differential gene expression was calculated by correlating Salmon gene-level counts with the effective lengths of target transcripts between the primary tumors and LM via DESeq statistical software. Ingenuity Pathway Analysis (Qiagen) was utilized for prediction of upstream regulators and to determine pathways that were significantly enriched or lost in LM.

Results: Patient characteristics were reviewed and are illustrated in Table 1. Twenty-four of the 42 patients were male, demonstrating a male predominance. In this cohort, male patients exhibited more aggressive disease: 64% patients who died and 74% who developed LM were male. Heat map and principal component analysis both demonstrated notable clustering of distinct genes in primary tumors and LM (Figure 1). In four patient-matched pairs, the primary tumors from different patients exhibited more similarities than the primaries shared with their own LM. Clear, defined clusters of upregulated genes not found in primary tumors were observed in LM. Pathway analysis revealed upregulation of 24 genes involved in cell motility and migration in the LM samples. Gene network reconstruction predicted androgen receptor (AR) as an upstream regulator of some of the most highly upregulated genes in LM (Figure 2).

Conclusion: Our data supports the hypothesis that significant genetic changes occur during the metastatic process and may be prime targets for new therapies. For the first time, upregulation of the AR pathway was identified in metastatic tissue. This novel finding is particularly promising in the context of OS. Identification of AR pathway upregulation in human LM tissue samples may provide a target for novel therapeutics for patients resistant to conventional chemotherapy.

Table 1: Patient demographics.

Sample ID	Sample Type	Sex	Living Status	Age at Dx	% Tumor Cellularity
OS-01-LM1	lung met	M	Deceased	15	50
OS-01-LM2	lung met	M	Deceased	15	50
OS-02-LM	lung met	M	Alive	5	90
OS-04-R(M)	primary (met'd)	M	Alive	14	90
OS-05-LM	lung met	M	Deceased	16	60
OS-06-LM	lung met	M	Deceased	17	60
OS-10-LM	lung met	M	Deceased	17	90
OS-10-R(M)	primary (met'd)	M	Deceased	17	60
OS-14-R (L)	primary	F	Alive	9	60
OS-15-R(L)	primary	F	Alive	15	90
OS-17-B(M)	biopsy (met'd)	M	Deceased	14	20
OS-17-LM	lung met	M	Deceased	14	80
OS-17-R(M)	primary (met'd)	M	Deceased	14	80
OS-25-R(L)	primary	F	Alive	15	70
OS-27-B(L)	biopsy (met'd)	F	Alive	15	60
OS-28-R(L)	primary	F	Alive	16	40
OS-38-B(L)	biopsy	F	Alive	38	60
OS-40-B(L)	biopsy	M	Alive	13	50
OS-41-R(M)	primary (met'd)	F	Deceased	77	90
OS-42-R(M)	primary (met'd)	F	Deceased	84	80
OS-43-R (L)	primary	M	Alive	63	50
OS-44-R (M)	primary (met'd)	F	Alive	29	80
OS-45-C (L)	recurrence	F	Deceased	60	80
OS-45-C(L)2	recurrence	F	Deceased	60	80
OS-45-R (L)	primary	F	Deceased	60	80
OS-46-R (M)	primary (met'd)	F	Alive	23	80
OS-47-R (M)	primary (met'd)	M	Alive	54	80
OS-48-R (L)	primary	F	Alive	83	80
OS-49-R (M)	primary (met'd)	M	Alive	18	80
OS-50-LM	lung met	M	Deceased	69	80
OS-51-LM	lung met	F	Deceased	45	80
OS-51-R (M)	Primary	F	Deceased	43	80
OS-52-R (L)	primary	F	Deceased	86	80
OS-53-R (L)	primary	M	Alive	32	90
OS-54-R (L)	primary	M	Alive	16	90
OS-55-R (M)	primary (met'd)	M	Deceased	75	90
OS-56-R (M)	primary (met'd)	M	Deceased	14	90
OS-57-C(M)1	recurrence (met'd)	M	Deceased	59	100
OS-57-C(M)2	recurrence (met'd)	M	Deceased	59	70
OS-57-LM	lung met	M	Deceased	59	100
OS-57-R (M)	primary (met'd)	M	Deceased	59	90
OS-58-R(M)	primary (met'd)	F	Deceased	19	70

Fig 1: Heat map and principle component analysis (PCA) demonstrate that the lung metastases demonstrate distinct changes in differential gene expression levels compared to the primary tumors.

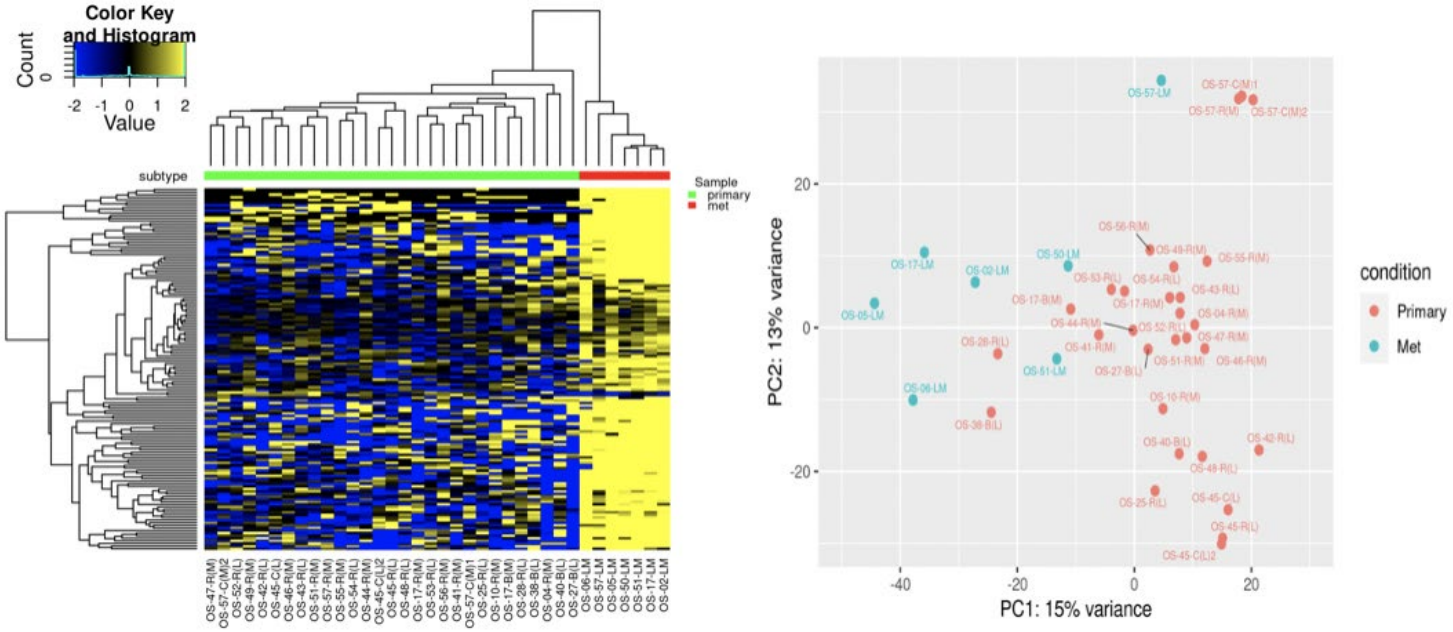
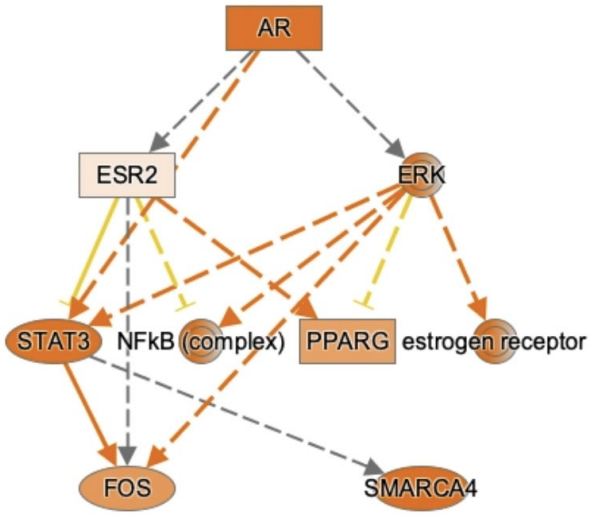


Fig 2: Ingenuity pathway analysis demonstrates Androgen Receptor as an upstream regulator in lung metastases of osteosarcoma patients.



Poster #086 3460952

EVALUATION OF CIRCULATING TUMOR CELLS IN RECURRENT OSTEOSARCOMA PATIENTS TREATED ON A PHASE II TRIAL OF GEMCITABINE AND NAB-PACLITAXEL: A REPORT FROM THE NATIONAL PEDIATRIC CANCER FOUNDATION

Masanori Hayashi[1], *Javier Oesterheld*[2], *David Loeb*[3], *Damon Reed*[4], *Leo Mascarenhas*[5], *Michael Isakoff*[6], *Bhuvana Setty*[7], *Joanne Lagmay*[8], *Emi Caywood*[9], *Eric Sandler*[10], *Matteo Trucco*[11], *Christine Pratilas*[12], *Tiffany Smith*[13], *Brooke Fridley*[4], *Lars M. Wagner*[14]

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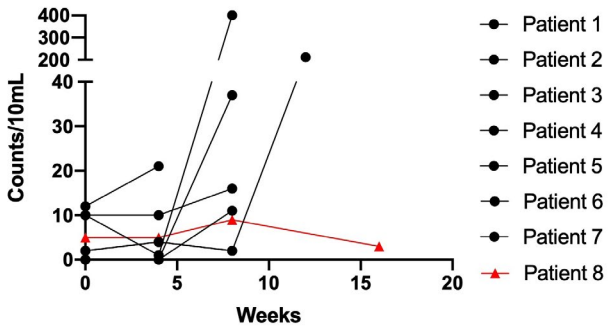
Objective: Hematogenous metastases are the leading cause of death in osteosarcoma patients, and identification of individual circulating tumor cells could potentially improve assessment of tumor response to therapy. Previous single-institutions studies have identified osteosarcoma cells in peripheral blood using a variety of techniques. However, little data is available regarding the feasibility and utility of sequential monitoring of relapsed osteosarcoma patients undergoing uniform treatment and imaging evaluations on a multi-institutional trial. As part of a phase II study of combined gemcitabine and nab-paclitaxel in patients with recurrent osteosarcoma, we prospectively collected peripheral blood samples to assess for circulating tumor cells at the start of each cycle of therapy.

Methods: Patients received gemcitabine and nab-paclitaxel on days 1, 8, and 15 of a 4-week cycle. All patients had measurable disease at enrollment, and responses were assessed by imaging after every two cycles. Ten ml of blood was collected in a CellSave™ tube at the start of study treatment and again with each subsequent cycle. The CellSieve™ microfiltration system was used to identify tumor cells based on size, with morphology and antibody staining used to confirm the presence of malignant cells.

Results: Fourteen patients (median age 15 years; range 12-24) with recurrent osteosarcoma were treated at one of 9 different institutions. All 14 patients had circulating tumor cells identified, including 12 at the time of study entry. Paired samples collected at study entry and while on therapy were available for 11 patients. An increase in circulating tumor cells was noted in 6 (86%) of the 7 patients who came off study for disease progression. In addition, a decrease in circulating tumor cells from study entry to the fourth cycle was noted in the one patient experiencing a partial response.

Conclusion: Circulating tumor cells can be identified in patients with recurrent osteosarcoma who have measurable disease. For many of these patients, the quantifiable changes in circulating tumor cells paralleled disease progression or response to treatment. The use of a low-pressure microfiltration system to identify tumor cells based on size exclusion was feasible in this multi-institution study. This approach allows for collection of tumor cells for further molecular analysis, and may potentially have a role for disease monitoring. A larger analysis using this methodology is ongoing in other sarcoma subtypes.



Depiction of number of circulating tumor cells over time for 7 patients with progressive disease (●) and one patient with partial response (Δ). Patients 2 and 7 had similar values at all time points.

Poster #087 3461000

UBIQUITIN-LIGASE ATROGIN MEDIATES ADAPTATION TO KIT TARGETED INHIBITION IN GASTROINTESTINAL STROMAL TUMOR

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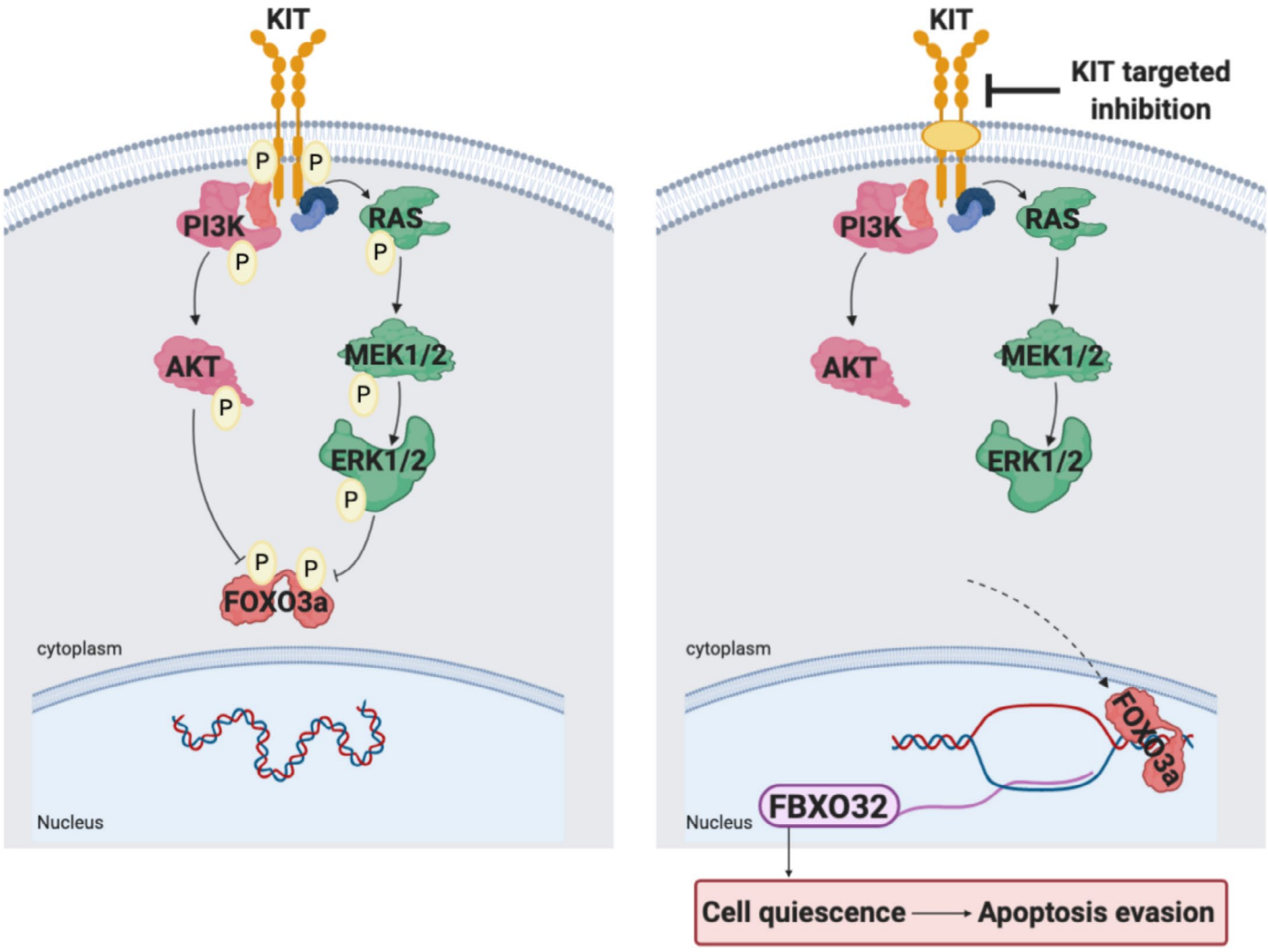
Objective: GIST is the most common mesenchymal tumor, arises from the interstitial cells of Cajal and displays myogenic features. Gain-of-function mutations in KIT are the most common initiating events and KIT oncogenic signaling is essential throughout the course of the disease. KIT inhibition with first-line imatinib (IM) provides a major clinical benefit in patients, but complete responses are rare. Resistance to IM mostly occurs due to polyclonal expansion of subpopulations harboring KIT secondary mutations. Interestingly, KIT oncogenic signaling is largely driven by PI3K/mTOR and RAS/MAPK pathways regardless of KIT primary or secondary mutations. Hence, dissection of KIT-downstream pathways may result in the identification of novel therapeutic vulnerabilities to maximize response to KIT inhibition.

Methods: Using clinically-representative human GIST cell models, we undertook pharmacological screenings, including cell viability, immunoblot, apoptosis induction and proliferation, to identify critical targetable nodes within PI3K/mTOR and RAS/MAPK pathways. Transcriptomic analysis (RNAseq) were used to discover genes co-regulated by KIT and KIT-downstream pathways. Functional studies, such as immunofluorescence, chromatin immunoprecipitation (ChIP), cell viability, flow cytometry and proliferation were performed on viral gene overexpression and knock-down cell models to elucidate Atrogin regulation and its biological role in GIST. Atrogin as biomarker of KIT inhibition was evaluated by immunohistochemistry (IHC) in pre- and post-IM tumor samples. Therapeutic inhibition of the ubiquitin proteasome system (UPS) was performed in vitro and in vivo.

Results: PI3K/mTOR and MEK1/2 were the most essential KIT-downstream nodes within PI3K/AKT/mTOR and RAS/MAPK pathways, respectively. Although single node inhibition impacted on cell proliferation and apoptosis induction, this effect was not sustained over time. However, simultaneous intermittent ablation was synergistic and well tolerated, showing prolonged anti-tumor effect in vitro and in vivo, thus supporting the critical role of these two pathways irrespective of the type of KIT mutation.
RNAseq underscored Atrogin (aka FBXO32, a SCF E3 ubiquitin-ligase and the main effector of muscular atrophy in cachexia) as the most differentially expressed gene co-regulated by PI3K/mTOR and RAS/MAPK, resulting in increased expression upon inhibition of KIT or KIT-downstream pathways. Functional studies and ChIP demonstrated that KIT and/or KIT-downstream signaling regulates FOXO3a, which in turn activates transcriptionally atrogin expression. Atrogin proved to have a pro-survival role in GIST. Knock-down and over-expression studies demonstrated in vitro and in vivo that atrogin leads to apoptosis evasion and treatment adaptation upon KIT or conjoined PI3K/mTOR and MEK1/2 inhibition through induction of cell quiescence. Atrogin function was restricted to GIST cell lineage, being absent in other KIT-driven tumor models. Moreover, a significant increase in Atrogin expression was shown in post-IM GIST tumor samples compared to pre-IM in the gene set database from the phase II RTOG-0132 trial, and also by IHC in a tissue microarray from 92 pre- and post-IM GIST samples. Finally, combined inhibition of KIT and the UPS inhibitor TAK-243 (an UAE specific inhibitor) showed enhanced anti-tumor activity compared to single-agent imatinib.

Conclusion: PI3K/mTOR and MEK1/2 are the critical mediators of KIT oncogenic signaling in GIST, and their intermittent co-inhibition is therapeutically effective independently of KIT mutational status. Atrogin emerges as a crucial KIT-dependent and GIST cell lineage-specific pro-survival factor, leading to adaptation to KIT targeted inhibition through induction of cell quiescence. Atrogin highlights UPS as a therapeutic vulnerability and combined KIT and UPS inhibition results in a novel therapeutic strategy to overcome tumor cell adaptation in the treatment of GIST patients.


KIT
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ERK1/2
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FOXO3a
cytoplasm
Nucleus
KIT
KIT targeted inhibition
PI3K
RAS
AKT
MEK1/2
ERK1/2
cytoplasm
FOXO3a
Nucleus
FBXO32
Cell quiescence
Apoptosis evasion

Poster #088 3461083

BONE METASTASIS OF GASTROINTESTINAL STROMAL TUMOR: CASE REPORT AND REVIEW OF THE LITERATURE

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[1]*Oncology, Universitary Hospital, Besançon, FRANCE;* [2]*Radiology, Universitary Hospital, Besançon, FRANCE;* [3]*Pathology, Universitary Hospital, Nancy, FRANCE;* [4]*Pathology, General Hospital, Belfort-Montbéliard, FRANCE;* [5]*Pathology, Universitary Hospital, Besançon, FRANCE;* [6]*Orthopedic surgery, Universitary Hospital, Nancy, FRANCE;* [7]*Visceral Surgery, Universitary Hospital, Besançon, FRANCE*

Objective: Gastrointestinal stromal tumors (GIST) are the most common primary mesenchymal tumor. Usually, elective metastasis sites are the liver and the peritoneum. However, no therapeutic standard exists for the management of bone metastases due to its very low incidence.

Methods: We report an atypical localization of a jejunal GIST: the case of a seventy-two years old woman with jejunal GIST resected in 2013 and followed up with adjuvant imatinib 400 milligrams until 2016. She presented in 2018 a unique humeral bone lesion which biopsy examination confirmed diagnosis of a GIST metastasis. Conservative surgery (resection-reconstruction with intercalary allograft) was achieved after five months neoadjuvant imatinib 400 milligrams and pathologists confirmed the satisfying histological regression and the complete resection. Afterward, the patient continued imatinib at the same dose daily. On the 21st of April 2020, she fully recovered after a functional education program with no recurrence observed until now.

Results: In the review of the literature and published case reports, bone metastasis of GIST is one of the rarest localizations (about 1%) and mainly occurs in the spine. Patients with GISTs of the small intestine and stomach suffered from bone metastasis more frequently and earlier than patients with GISTs in other primary sites. If isolated, the median overall survival is better than that of liver metastasis. It happens on average four years after the primary, until twenty years for some cases, proving the need for a long-term clinical and radiological follow-up.

Standards of care recommendations are not established, but oral medication involving TKI drug class should be proposed, depending on molecules previously received. Elective metastatic surgery or stereotaxic radiotherapy depending on patient characteristics/operability might also be discussed.

Conclusion: Bone metastasis of GIST is one of the rarest localizations. Management requires multidisciplinary collaboration (medical oncologist, radiation oncologist, surgeon, pathologist, radiologist). Our patient may have had a conservative surgery after several months of imatinib. A year and a half later, she is still in complete remission.

Poster #089 3461140

FIVE-YEAR SURVIVAL OF A PATIENT WITH DEDIFFERENTIATED CHONDROSARCOMA TREATED WITH CHEMOTHERAPY AND JOINT SPARING SURGERY

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Objective: Outcomes in patients with dedifferentiated chondrosarcoma are extremely poor. Five-year survival is approximately 13% and most patients are not alive two years after diagnosis. Wide surgical margins are required to prevent local recurrence and provide a favorable outcome. Chemotherapy remains controversial but has shown some promise in certain studies. Options for reconstruction of the proximal humerus include prosthetic and osteoarticular allograft reconstruction with resection of the articular surface of the humerus. In a young, high-demand patient, an articular surface sparing procedure is more durable and less likely to need revision over time. The purpose of this report is to describe a case of non-metastatic dedifferentiated chondrosarcoma that underwent joint sparing surgery with five-year follow-up including functional outcomes.

Methods: A right-hand dominant 29-year-old male was found to have a dedifferentiated chondrosarcoma of his proximal humerus (Figure 1A and B). Staging studies demonstrated no evidence of metastatic disease. The patient underwent a joint preserving resection of the tumor with reconstruction with a hemicortical allograft. This involved resection of the pectoralis insertion, cephalic vein, proximal long head of the biceps tendon, insertion of the entire rotator cuff, and the anterior third of the deltoid muscle. The bone was resected at the anatomic neck of the humerus with preservation of the articular surface and medial cortex. Reconstruction of the rotator cuff was performed utilizing a dermal allograft (Figure 2). Post-operatively, he underwent adjuvant chemotherapy with doxorubicin, cisplatin, and ifosfamide for 7 rounds over an 8-month period. He remained in a shoulder immobilizer with no shoulder motion for 6 weeks and then started a rotator cuff rehabilitation protocol. He stated active-assist and passive range of motion at 6 weeks and was allowed to start light weight bearing 3 months after surgery. At 6 months after surgery he was allowed to be full weight bearing without limitations.

Results: Final pathology demonstrated a dedifferentiated chondrosarcoma with a high-grade spindle cell component measuring 3.5 x 2.5 x 2.0 cm in size (Figure 3). A minimum of a 1 cm margin was achieved, and no surgical complications occurred. At one-year he had 40 degrees of active abduction of the shoulder, 20 degrees of forward flexion and 45 degrees of external rotation with full passive range of motion. His Musculoskeletal Tumor Society (MSTS) score was 28, Quick DASH was 20.5 and Constant and Murley was 35. Five years after surgery his active motion has improved to 65 degrees of abduction, 45 degrees of forward flexion, and 60 degrees of external rotation. His current MSTS score is 29, losing one point for hand positioning ability. His Quick DASH is 2.3 and Constant and Murley is 80. He is pain-free and able to work as an Orthopaedic Surgeon. He has returned to back country skiing, sport climbing, mountaineering and search and rescue. There is no evidence of local recurrence of metastatic disease at five-year follow-up and the allograft has incorporated without evidence of failure (Figure 1C).

Conclusion: Obtaining adequate margins is the most important step in the surgical treatment of dedifferentiated chondrosarcoma, and the authors believe that articular sparing surgery should only be attempted when a wide margin can be obtained. In this case, joint preserving surgery was able to be performed while still obtaining a 1 cm margin. The patient's survival is likely due to the small size of the tumor, adequate margins with surgical resection and completion of adjuvant chemotherapy. The patient's functional outcomes are on the high end compared to the reported outcomes of prosthetic reconstructions and improved compared to osteoarticular allograft reconstructions. These functional outcomes have continued to improve over time and the patient has been able to have an active lifestyle and continue his career as a surgeon.

Figure 1: A) Initial AP and axillary radiographs of the right shoulder. The arrows demonstrate a lytic area involving the lateral aspect of the proximal humerus with a periosteal reaction. (B) Initial coronal T1- and T1-contrast enhanced MRI's of the right shoulder demonstrating a tumor involving the proximal humerus with cortical breakthrough and an associated soft tissue mass. C) Radiographs at final follow-up. AP and lateral radiographs of the proximal humerus demonstrate incorporation of the allograft. The osteotomy site is no longer visualized and there is remodeling of the bone. The articular surface of the humerus is preserved.

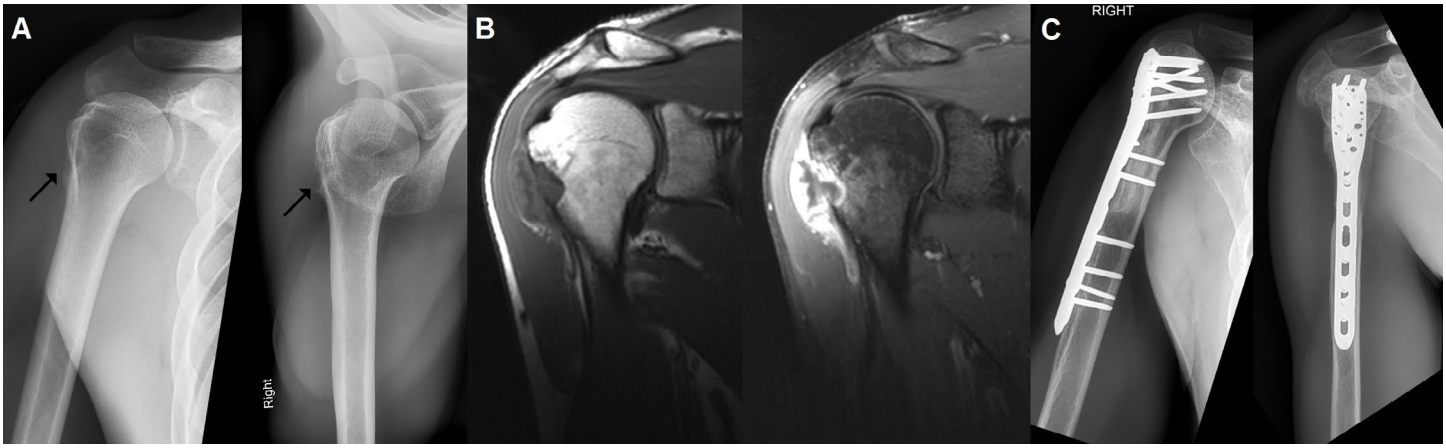


Figure 2: A) Intraoperative photograph of the proximal humerus after fixation of the allograft to the host bone. A dermal allograft was placed under the plate proximally to provide a surface for repair of the rotator cuff. The articular surface was able to be preserved. (B) Intraoperative photograph of the proximal humerus after repair of the rotator cuff to the dermal allograft. Sutures were also placed through the plate for added fixation.

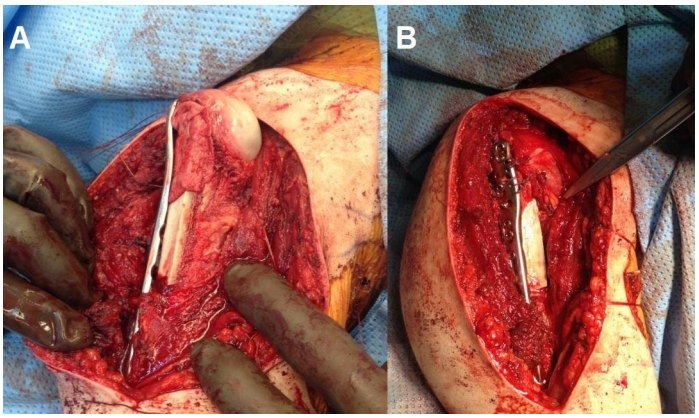
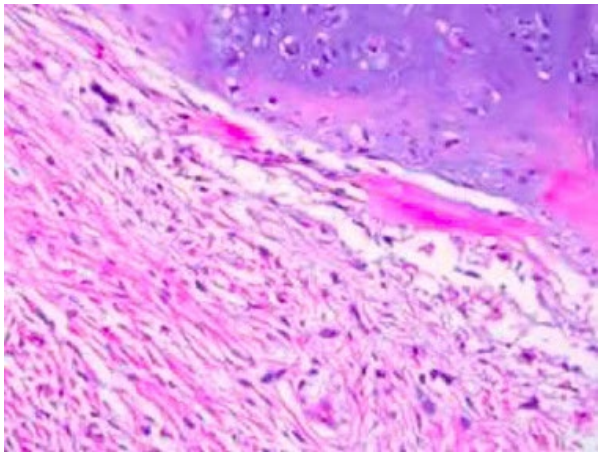


Figure 3: Histopathology slide of the operative specimen. A low-grade chondrosarcoma in the upper right is juxtaposed with a high-grade spindle cell sarcoma in the lower left consistent with a dedifferentiated chondrosarcoma.



Poster #090 3461203

IMPACT OF IMMUNOTHERAPY AND TARGETED THERAPY ON TUMOR GROWTH RATE IN SARCOMA

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[2]*Division of Medical Oncology, Princess Margaret Cancer Centre, Toronto, Ontario, CANADA*

Objective: Sarcomas are a heterogeneous group of tumors, and there is varying tumor growth kinetics between different sarcoma subtypes and compared with other solid tumors. With the increasing use of immunotherapy and targeted treatments in oncology, it is essential to understand the biological effects of these therapies on tumor kinetics. Hyperprogressive disease (HPD) is a phenomenon defined as an accelerated tumor growth rate (TGR) in a subset of patients who received Immunotherapy during initial radiological evaluations. HPD has been reported in mixed solid tumors (Champiat et al. 2017), non-small cell lung cancer (Ferrara et al. 2018), and head &neck cancer (Saada-Bouzid et al. 2017). The primary objectives of the study are to assess the TGR of sarcoma patients on targeted therapy or immunotherapy and to determine the prevalence of HPD in the study population. The secondary objectives are to correlate the TGR on therapy with survival outcomes and to assess any association with patient clinicopathological characteristics to identify this subgroup of patients who have a worse outcome.

Methods: We performed a retrospective review of advanced sarcoma patients enrolled in immunotherapy or targeted therapy clinical trials at the Princess Margaret Cancer Centre, Toronto. Patient demographics, disease characteristics, Royal Marsden Hospital (RMH) prognostic score, treatment modalities, side effects and survival outcomes were collected for eligible patients. TGR was assessed for each patient based on serial CT scans at pre-baseline, baseline and on treatment timepoints. TGR was calculated using a published formula (Champiat et al. 2017), and the ratio between reference and experimental groups was then calculated. The predictive accuracy of HPD was assessed using Cox proportional hazards analysis both as a continuous variable and using a cut-off for the TGR ratio percentage of more than 50%. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier (log-rank) analysis. Statistical significance was defined as $p<0.05$.

Results: We identified 146 patients who were treated with immunotherapy, targeted therapy, or combination chemotherapy and targeted therapy between July 26, 2013, and August 7, 2018. 106 patients met the eligibility criteria. 20 patients received single or combination immunotherapy, 86 patients received targeted or combination chemotherapy and targeted therapy (Table 1). The overall incidence of HPD in our study was 4.7%. Three patients from the immunotherapy group had HPD (15%), and two patients from the non-immunotherapy group had HPD (2.3%). The hazard ratio for the patients with TGR ratio percentage of ≥50%(HPD) was 9.34 (95% CI 3.38-25.84, p = < 0.001). The median survival in all patients with HPD vs non-HPD was 3.9 months (95% CI 2.5-5.2 months) vs 16.1 months (95 % CI 13-19.2 months), respectively ($p<0.001$) (Figure 1). A higher proportion of new metastatic lesions was seen among HPD patients ($p=0.001$), but no association with age, ECOG, sex, RMH prognostic score, combination immunotherapy, grade 3/4 side effects or clinically significant adverse events (CSAEs) was found. There was no interaction between HPD and receipt of immunotherapy vs other therapy.

Conclusion: There is a correlation between TGR and clinical outcomes in patients with sarcoma treated with immunotherapy or targeted therapy. HPD is associated with worse survival outcomes and may serve as a useful tool in the assessment of treatment futility during patient therapy.

PATIENTS' CHARACTERISTICS (N=106)

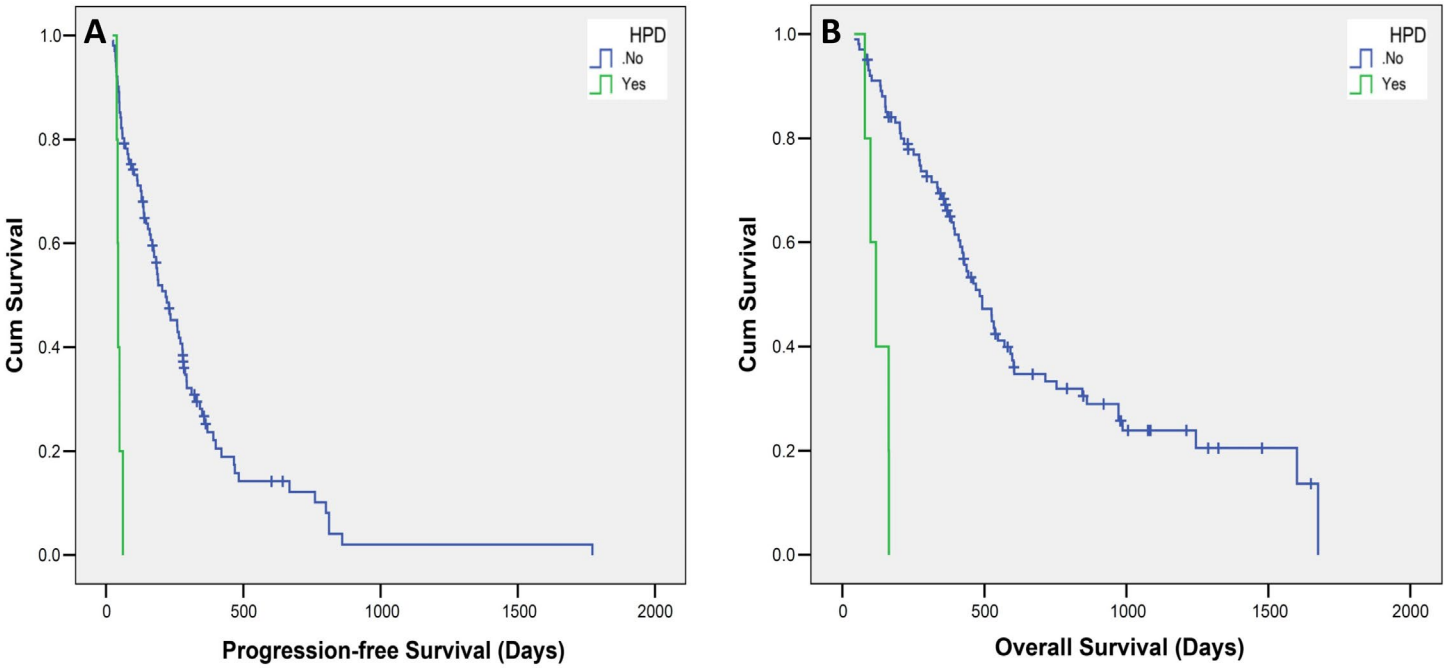
Variable	**N**	**%**
Age (years), median (range)	54 (21-86)	NA
Gender (Male: Female)	49:57	46%:54%
Tumor Histology		
Liposarcoma (LPS)	32	30%
Leiomyosarcoma (LMS)	26	24.5%
Alveolar soft part sarcoma (ASPS)	9	8.50%
Undifferentiated pleomorphic sarcoma (UPS)	8	7.50%
Gastrointestinal stromal tumor (GIST)	7	6.60%
Clear cell sarcoma	4	3.70%
Others	20	18.80%
ECOG 0:1	35:71	33:67%
Study phase I/II/III	59/18/29	56%/17%/27%
RMH score (0-1):(2-3)	71:35	67%:33%
Treatment Type		
Single IO:Combination IO (N=20)	11:9	10.3%:8.5%
Targeted treatment (TT) (N=54)		
Pan-kit Inhibitors	7	6.60%
Nucleopore inhibitor (NI)	35	33%
Antiangiogenic TKI (ATKI)	4	3.80%
MDM2/CDK inhibitors	8	7.50%
Chemo&Targeted Therapy (CTX + TT) (N=32)		
Doxorubicin + ATKI : Doxorubicin + NI	12:20	11.3%:18.8%
Patients characteristics with HPD		
Tumor type (N=5)	**Type of treatment**	**TGR Ratio %↑**
LMS (N=1)	Combination IO	144%
UPS (N=1)	Single IO	84%
Clear cell sarcoma (N=1)	Single IO	71%
LMS (N=1)	CTX & TT	61%
LPS (N=1)	TT	57%

NA, not applicable; ECOG, Eastern Cooperative Oncology Group; RMH, Royal Marsden Hospital; IO, immunotherapy; ATKI, Antiangiogenic tyrosine kinase inhibitors; HPD, Hyperprogressive disease.

Figure 1: Kaplan-Meier curves of PFS and OS for HPD vs Non-HPD patients

Figure 1A: PFS for HPD patients vs Non-HPD; HR 7.90 (95% CI 2.90-21.53; p<0.001).

Figure 1B: OS for HPD patients vs Non-HPD; HR 9.35 (95% CI 3.38-25.84; p<0.001). The median survival in all patients with HPD vs non-HPD 117 days (3.9 months) (95% CI 2.5-5.2 months) vs 483 days (16.1 months) (95 % CI 13-19.2 months).



Poster #091 3461252

PRIMARY SITE SURGERY IS ASSOCIATED WITH IMPROVED SURVIVAL IN METASTATIC SOFT TISSUE SARCOMA OF THE EXTREMITY

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Objective: Systemic therapy is viewed as the cornerstone of therapy for metastatic soft tissue sarcoma (STS) of the extremity, with a limited role for local surgical therapy. The objective of this study was to assess the impact of surgery on survival outcomes among patients with stage IV extremity STS.

Methods: Utilizing the National Cancer Database, we identified 12,848 patients with extremity STS presenting with synchronous metastases from 2004-2015. Inclusion criteria included age ≥ 18, tissue diagnosis of extremity STS based on ICD-O-3 coding, and complete staging data. Patients were grouped by treatment modality (chemotherapy, radiotherapy (RT), surgery). Survival between groups was compared using the Kaplan Meier method and log rank test. Cox proportional hazard analysis was conducted to identify multivariate predictors of survival on all patients, and included age, sex, race, facility type, Charlson-Deyo score, histology, grade, tumor size, location of metastases, and treatment. Landmark analysis was conducted on all patients surviving greater than 4 months, including repeat Cox proportional hazard analysis.

Results: The mean age of the cohort was 57.6 years and 55.7% were male. The most common histologies were leiomyosarcoma (18.3%) and vascular sarcomas (7.8%). 59.0% of patients presented with lung metastases. 23.6% of patients had chemotherapy only, 11.4% primary site surgery only, and 8.3% RT only. 13.4% received surgery and chemotherapy, 10.6% chemotherapy and RT, 6.4% surgery and RT, and 7.7% tri-modality therapy. 18.5% received no treatment. Median survival for the entire cohort was 9.5 months, ranging from 9.1 – 10.9 months by year of diagnosis ($p > 0.05$). Survival for patients having primary site surgery was 15.2 months ($p < 0.001$). On multivariate analysis, surgery ($p = 0.003$), RT ($p = 0.002$), and chemotherapy ($p = 0.021$) were independently associated with significantly improved survival. Among patients receiving chemotherapy, surgical resection of the primary site remained associated with improved survival ($p = 0.009$). Trends analysis revealed that the use of chemotherapy increased over the 12-year study period, while the use of surgery and RT decreased. On landmark analysis of patients surviving greater than 4 months, surgery ($p = 0.001$), radiation ($p = 0.001$) and chemotherapy ($p=0.004$) were all associated with increased overall survival on multivariable analysis.

Conclusion: Among patients with stage IV extremity STS, surgical resection of the primary site is associated with improved survival, especially in the context of multimodality therapy. Further evaluation of the potential for surgery to benefit subsets of patients with stage IV extremity STS appears warranted.

Poster #092 3461276

CHARACTERIZATION OF TUMOR INFILTRATING IMMUNE CELLS FROM ADULT SOFT TISSUE SARCOMAS

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Objective: Sarcoma is a group rare soft tissue and bone tumors with over 50 distinct subtypes. Survival rate ranges widely due to the lack of efficacious treatments. Immunotherapy, such as adoptive cell therapy (ACT), has drawn much interest due to its minimal toxicities. In ACT, tumor infiltrating lymphocytes (TILs) are isolated from a patient, expanded, and autologously infused back to the patient. Clinical response to ACT varies across patients and subtypes, and further research is necessary to improve outcomes. We recently observed the presence of TILs in Undifferentiated Pleomorphic Sarcoma (UPS) and Myxofibrosarcoma (MFS), and that PD-L1 overexpression in UPS is correlated with better clinical outcome but not in MFS (Wunder et al., OncoImmunology, 2020). The Th1 inflammatory pathway was identified to be highly activated in the former but not the latter cohort, which may explain the better clinical outcome. These results illustrate the differences where TILs may play a critical role. Sarcoma TILs are difficult to culture, and their role in UPS and MFS remains largely unstudied. We hypothesize that there are phenotypic and functional differences between TILs of UPS and MFS primary tumors that may be related to clinical outcome. We first aim to robustly expand sarcoma TILs to sufficient numbers, and subsequently characterize TIL populations and cytokine profiles from UPS and MFS.

Methods: TILs are being expanded and cultured from 5 UPS and 5 MFS primary tumors with various PD-L1 levels. With the tumor fragment method of TIL culturing, bulk tumors were cut into 1mm fragments and seeded at 1 fragment per well in 2mL of complete media (CM). Majority of TIL cultures obtained less than 1x10^6 cells after 4 weeks in high IL-2 CM, which is insufficient for analysis. Rapid expansion protocol (REP) with anti-CD3/CD28 Dynabeads was employed to further expand these TILs. To investigate subtype-specific TIL's phenotypes and functions, cells will be characterized via flow cytometry with various immune cell panels (Eg CD4,8,25,56,68). Unbiased large-scale cytokine screening of TIL populations will be performed with the membrane detection assay. Cytokine secretion will be determined via intracellular cytokine staining, which would identify cell types responsible for their production. TILs and tumor cells would be cultured from selected cases and case-specific tumor PD-L1 expression will be determined via RT-qPCR. Co-culturing of TILs and tumor cells would elucidate subtype-specific TIL reactivity, and IFN-□/Granzyme B ELISA and Chromium Release Assay would be performed as indirect and direct tumor killing measurements, respectively.

Results: Sarcoma's exhibited sparse TIL counts, despite 4 weeks in CM cultures, may be due to its lower immune infiltration compared to other tumors, such as melanoma. Of 4 MFS cases processed to date, 15 TIL populations were derived and cultured, but the majority did not achieve sufficient cells for analysis (Fig 1). REP successfully expanded 14/15 TIL populations and obtained between 7.8 to 268 x10^6 cells (Tables 1&2; Figs 2&3).

Conclusion: Tumor immune environments of UPS and MFS are poorly understood. Sarcoma infiltrates are rare and difficult to culture, which impedes their characterizations and studies. These results demonstrate REP's capability in expanding the majority of TIL populations. We have established a robust method to expand TILs and obtained enough for downstream analysis. By further characterizing CD markers with flow cytometry and determining functional activities with cytokine profiling and cytotoxic assays, we hope to identify differences in immune infiltrates between distinct subtypes of UPS and MFS. Understanding these infiltrates and their relations with PD-L1 expression by tumors may allow researchers and clinicians to better recognize subtype-specific tumor immune environments, design drugs to modulate this environment more favorably, select more desirable infiltrates for ACT, and ultimately improve clinical outcomes.

Table 1. REP Treatment of Populations with High Initial Cell Count

Populations	Total Cells Seeded ($x10^6$)	Total Cells Collected ($x10^6$)	Fold-Expansion
TIL 164 1A	2.2	103.0	46
TIL 164 1B	1.4	146.0	103
TIL 207 1A	7.0	155.0	22
TIL 207 1B	7.0	268.0	38
TIL 225 1A	5.0	64.0	13
TIL 225 1B	4.0	33.5	8
TIL 207 1A (-)	2.0	8.0	4
TIL 207 1B (-)	2.0	12.7	6
TIL 225 1A (-)	2.0	4.5	2
TIL 225 1B (-)	2.0	4.3	2

REP treatment of populations with high initial cell count over 3 weeks. Graphed analysis shown in Figure 2. Populations that achieved ≥ 1x10^6 cells after 4 weeks of initial CM culturing were REP-treated with anti-CD3/ CD28 Dynabeads on 24-well plates over 3 weeks. At week 0 of REP, cells were seeded at 1x10^6 cells/ well, except for TIL 164 1A and TIL 164 1B which were seeded at 1.1x10^6 cells/ well and 1.4x10^6/ well, respectively. Populations were expanded with the addition of Dynabeads at a bead to cell ratio of 1:1. At week 3 post-REP, cells were collected, counted, and fold expansions were determined. Cell counts performed via hemocytometer. Negative controls (-) were allocated for certain populations with sufficient initial cell availability.

Table 2. REP Treatment of Populations with Low Initial Cell Count

Populations	Total Cells Seeded ($x10^3$)	Total Cells Collected ($x10^6$)	Fold-Expansion
TIL 164 2	175	7.8	45
TIL 207 2A	120	24.3	203
TIL 207 2B	500	59.6	119
TIL 214 1A	70	9.6	137
TIL 214 1B	60	17.0	283
TIL 214 2A	30	23.5	783
TIL 214 2B	25	20.6	824
TIL 225 2A	240	38.8	162
TIL 225 2B	290	n/a	n/a

REP treatment of populations with low initial cell count over 4 weeks. Graphed analysis shown in Figure 3. Populations that achieved <1x10^6 cells after 4 weeks of initial CM culturing were REP-treated with anti-CD3/ CD28 Dynabeads on 96-well plates over 4 weeks. At week 0 of REP, cells were seeded at 8x10^4 cells/ well, except for populations with <8x10^4 in total cells, which were seeded at total cells/well. For example, TIL214 1B was seeded at 6x10^4 cells/well. Populations were expanded with the addition of Dynabeads at a bead to cell ratio of 1:1; once at week 0 and once more as re-stimulation at week 2. At week 4 post-REP, cells were collected, counted, and fold expansion was determined. TIL225 2B did not yield any growth under 10X light microscope observation over 4 weeks of REP. Lack of cells and cell debris were observed, hence this population was not collected. Cell counts performed via hemocytometer. Negative controls were not established due to constraints with initial cell availability.

Figure 1. Initial culturing of 4 MFS TIL cases with complete media (CM) over 4 weeks. Ten total cases were selected, with five cases for each UPS and MFS sarcoma subtypes. To date, four MFS cases #164, 207, 214, and 225 have been processed. TIL populations were identified and categorized based on their growth rates, hence labeled as "1" or "2" representing "fast" or "slow" growing TILs, respectively. Additional populations "A" and "B" represent biological replicates. 15 populations were derived from the 4 MFS cases. Population TIL164 "2" had no replicates. Populations were cultured and expanded from tumor fragments in high IL-2 supplemented CM over 4 weeks in duration. At week 4, populations' cell counts were determined via hemocytometer. As shown, the 9 populations that achieved <1x10^6 cells at week 4 were further labeled with specific cell counts. 6 populations achieved ≥ 1x10^6 cells.

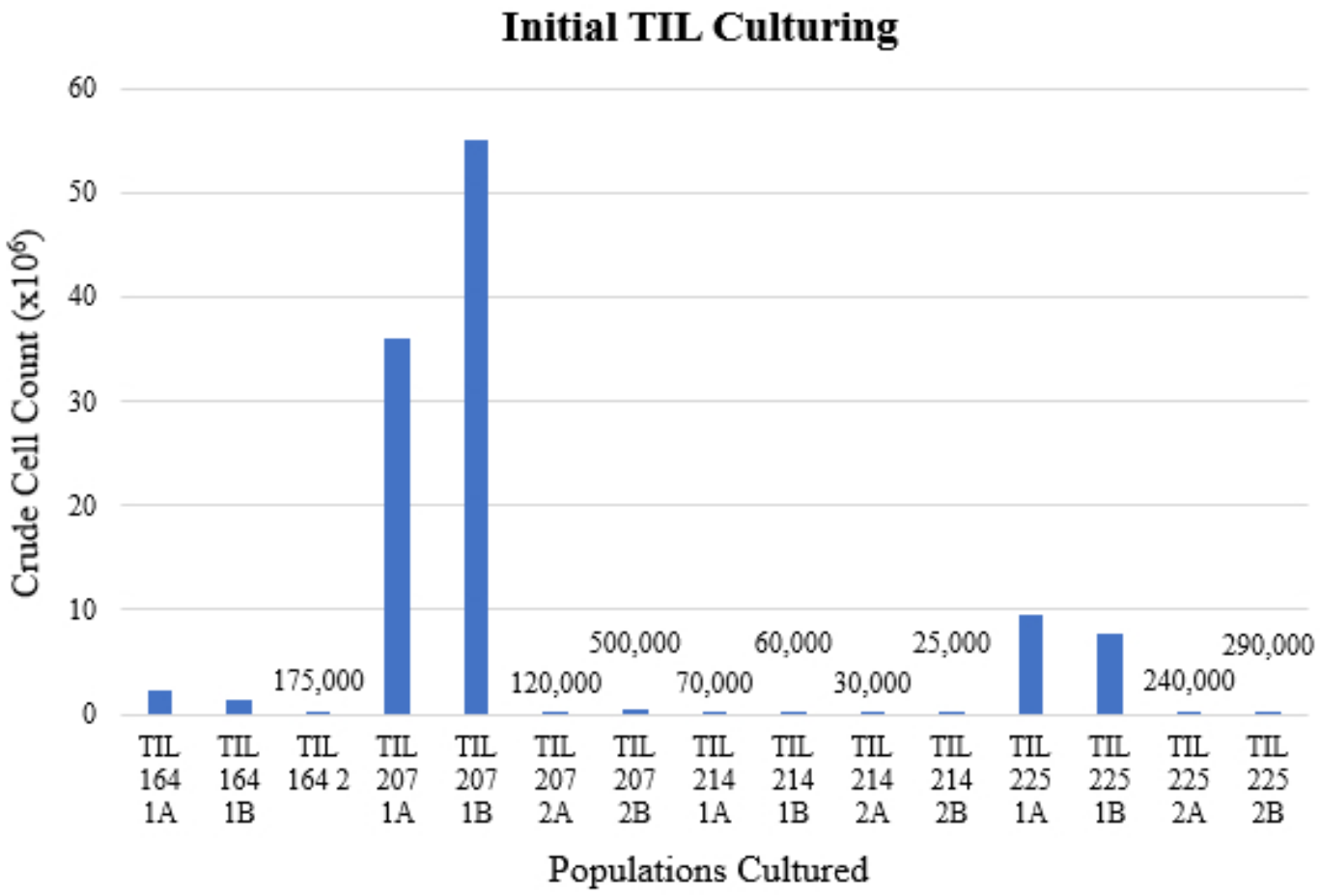


Figure 2. REP treatment of populations with high initial cell count over 3 weeks. This graph corresponds to Table 1. 6 out of 15 populations achieved ≥ $1x10^6$ cells after 4 weeks of initial CM culturing and were REP-treated on 24-well plates. All REP-treated populations have trendlines with positive slopes across the 3 weeks of REP expansion, indicating positive growth rates. All negative controls (-), without Dynabead treatments, have near-flat trendlines indicating lack of growth. REP was successful in expanding all 6 TIL populations. Cell counts performed via hemocytometer.

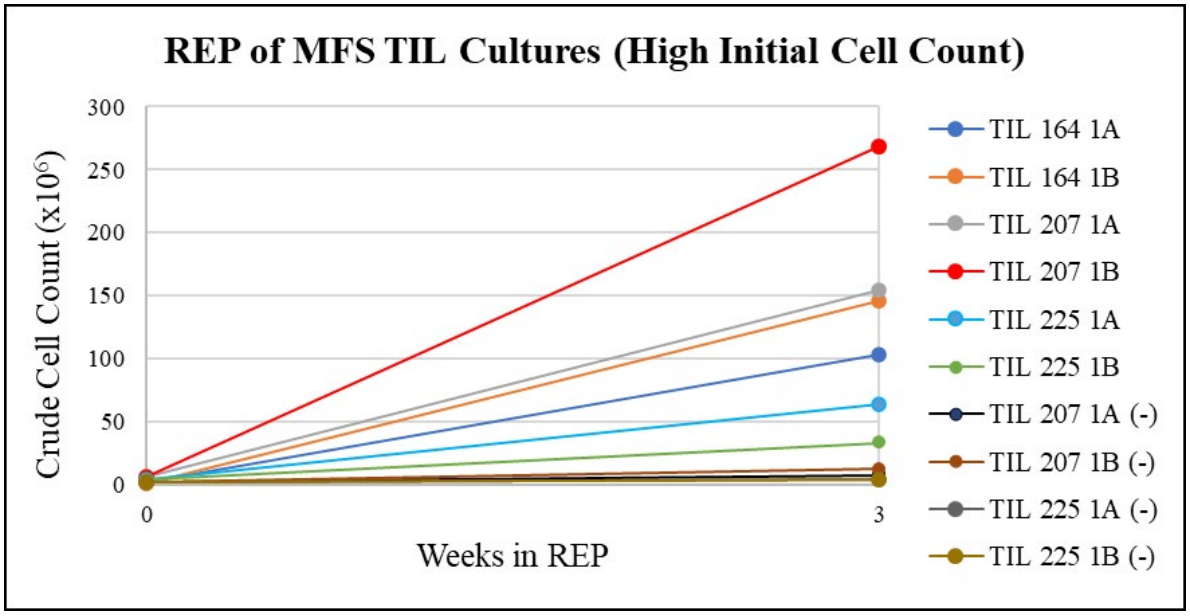
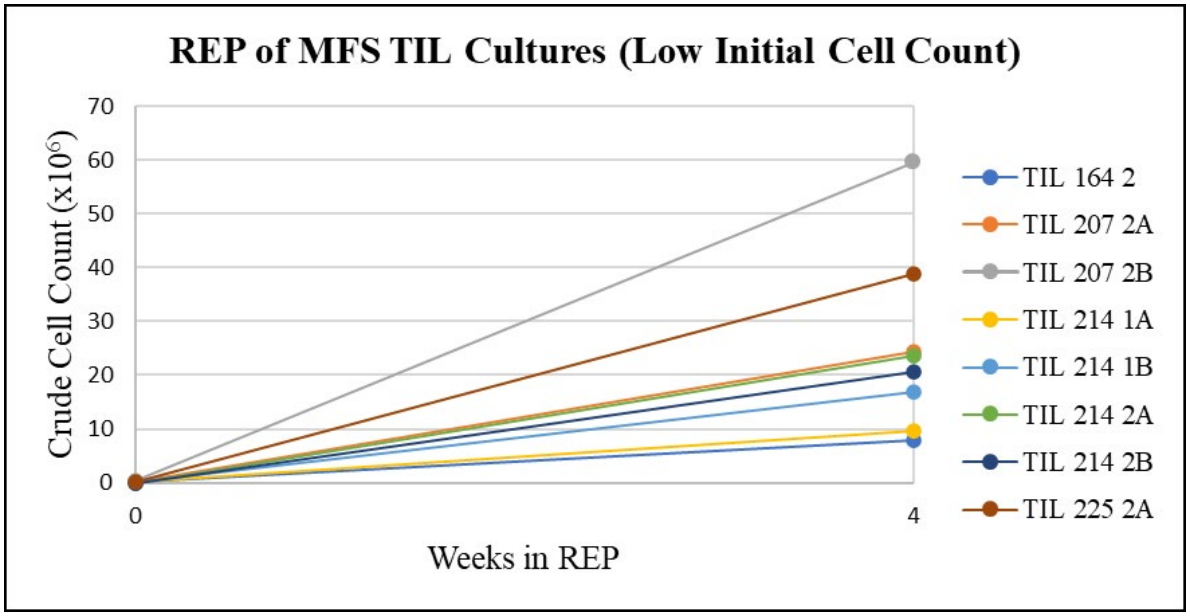


Figure 3. REP treatment of populations with low initial cell count over 4 weeks. This graph corresponds to Table 2. 9 out of 15 populations achieved <$1x10^6$ cells after 4 weeks of initial CM culturing and were REP-treated on 96-well plates. REP-treated populations have trendlines with positive slopes across the 4 weeks of REP expansion, indicating positive growth rates. REP was successful in expanding 8 of 9 TIL populations. TIL 225 2A failed to expand (data not shown), likely due to cell fatigue and apoptosis during initial 4 weeks in CM culture and not due to REP's robustness. Negative controls were not established due to constraints with initial cell availability. Cell count performed via hemocytometer.



Poster #093 3461301

IMPACT OF NEOADJUVANT CHEMOTHERAPY FOR RETROPERITONEAL SARCOMAS: A PROPENSITY BASED ANALYSIS OF A RETROSPECTIVE INTERNATIONAL, MULTICENTER COHORT

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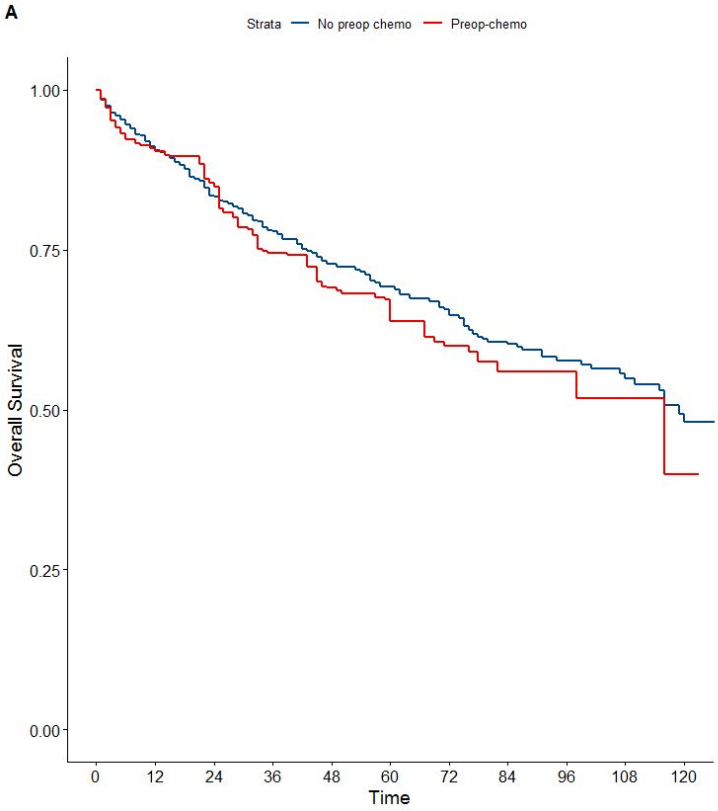
Objective: Surgery for retroperitoneal sarcoma (RPS) remains associated with a high local and in certain subtypes with a high systemic recurrence rate. The impact, if any of neo-adjuvant chemotherapy (NAC) on outcome is still unknown with inconclusive results. The objectiveof this report is to evaluate the impact of NAC on survival.

Methods: All patients operated for a histologically proven-RPS in the 8 centers of the Trans-Atlantic Australasian RPS Working Group (TARPSWG; Amsterdam, Boston, London, Mannheim, Milano, Paris, Toronto, Varsavia) were retrospectively identified. Principal factors guiding the use of NAC were used to develop a propensity score by logistic regression. Overall (OS) and disease-free (DFS) survival were studied after Inverse Propensity-score weighting (IPW) and after propensity score matching as a sensitivity analysis. Survival curves were calculated according to Kaplan-Meier and the Cox's model was used for the prognosis analysis.

Results: We identified 1007 patients. Mean age was 57(+/-14) years with 524(52%) of males. Tumors were mostly dedifferentiated liposarcoma 370(37%), well differentiated liposarcoma 236(26%), leiomyosarcomas 194(19%) and others 180(18%). Federation National des Centres de Luttes Contre le Cancer (FNCLCC) grades were 1 in 329(34%), 2 in 370(38%) and 3 in 267(27.6%). NAC was delivered in 152(15.1%) patients and rates of prescription per center varied from 2% to 30%. Factors associated with NAC administration were the size of the tumor (p<0.0001), age (p<0.0001), histological subtype (p<0.0001) FNCLCC grading system (p<0.0001) and invasion of adjacent organs (p<0.0001). Standardized differences between the NAC and no-NAC groups were adequately corrected by the score and only gender had a greater than 10% standardized differences after weighting. Median OS and DFS respectively were 116[107-NR] and 52[44-59] months. After IPW, NAC was not associated to a better OS (HR=1,68[1,19-2,35], p=0,003) or DFS (HR=1,35[0,97-1,86], p=0,07) (figure: left OS, right DFS). Propensity score matching was used as a sensitivity analysis and yield similar results. NAC also did not demonstrate any survival benefits when the analysis was restricted to the 267(27.6%) patients with grade 3 tumor (p=0.8) but the sample size was smaller. A subgroup of patient might benefit more from NAC but was not identified in this study. Multivariate analysis identified male sex (HR=1.92[1.35-2.75], p =0.0003), grade (e.g. 3 vs 1 HR=3.12[1.17-8.30], p=0.02) and of tumor (p=0.007) as prognosis factor for OS which could be used as stratifying factor in a future randomized trial.

Conclusion: In this retrospective study, NAC was not associated with any survival benefits despite the attempts to control for confounding factors. Randomized controlled trial like STRASS-2 will answer this question.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Preop-chemo
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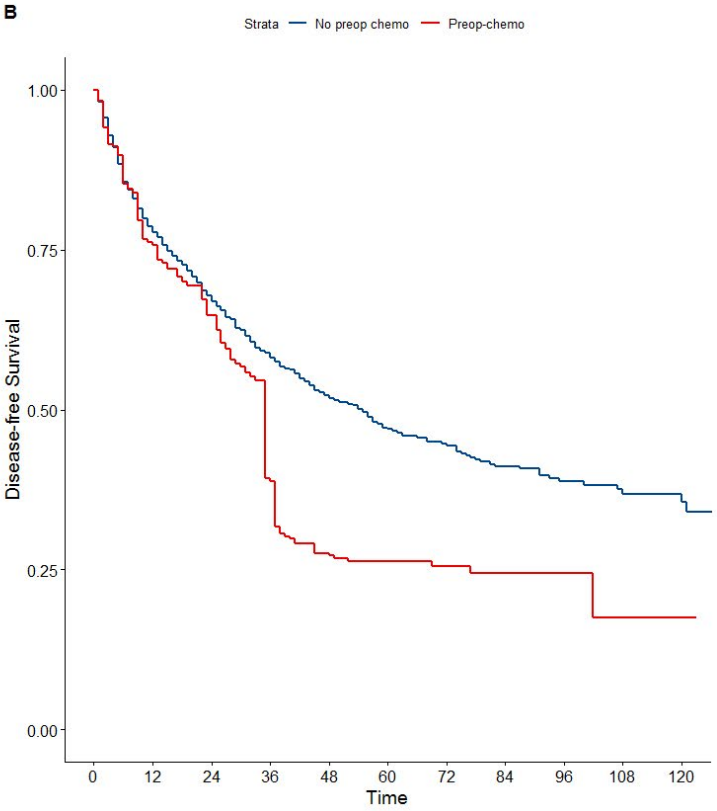
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Disease-free Survival
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Poster #094 3461333

SURGICAL MANAGEMENT OF PRIMARY LESION OF SOFT TISSUE SARCOMA MAY IMPROVE OVERALL SURVIVAL OF PATIENTS WITH INITIAL METASTASIS

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Objective: Approximately 10% of patients with soft tissue sarcoma have metastasis at initial presentation. It remains unclear whether the local treatment of primary lesion improves the overall survival of patients, especially for non-round cell soft tissue sarcoma, on which the effectiveness of chemotherapy is relatively limited. This clinical question is even more relevant when the complete resection of metastasis seems unattainable.
This study aims to investigate the outcome of local management for non-round cell soft tissue sarcoma patients with initial metastasis.

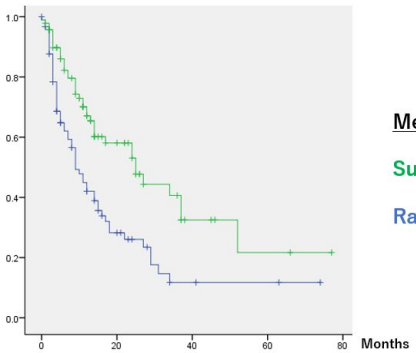
Methods: This retrospective analysis was based on the Japanese Nationwide Bone and Soft Tissue Tumor registry. The patients of non-round cell sarcoma with initial metastasis were enrolled, and their overall survival was compared among the type of surgical treatment of the primary lesion. Then, among the patients who did not receive metastasectomy, those who received wide/marginal-margin excision for primary lesion (Surgery group) and those who received radiotherapy alone (Radiotherapy group) were extracted. Characteristics of these two groups (age, sex, size, tumor origin, pathological grade, depth, with or without chemotherapy) were matched with the propensity score (PS) method. The overall survival was compared using the Kaplan-Meier method.

Results: In total, 983 records were eligible for analysis, with a median follow up of 10 months (range: 1-83). The median overall survival of the patients who received wide or marginal resection of the primary lesion were better than that of the patients who received no surgery (31 months (25.0-37.0), 25 months (17.5-32.5), and 14 months (11.0-17.0) respectively, P<0.05). Among them, Surgery group had 322 patients, and Radiotherapy group had 106 patients. With PS matching method, 92 cases from each group were matched. The median overall survival of Surgery group was significantly better than that of Radiotherapy group (25 months (15.3-34.7) vs 9 (6.1-11.9) months, P<0.001).

Conclusion: Surgical resection of the primary lesion with adequate margin may be associated with better prognosis in patients with metastatic non-round cell soft tissue sarcoma.

Kaplan-Meier: PS matched groups (92 cases each)

Surgery group (wide/marginal resection) resection is associated with better OS than Radiotherapy alone group

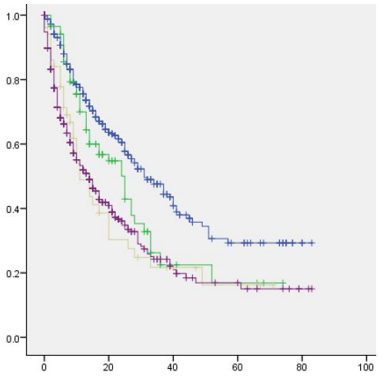


Median overall survival (month, 95%CI)	P<0.001*
Surgery (wide/marginal)	25.0 (15.3-34.7)
Radiation alnoe	9.0 (6.1-11.9)

* Log-rank test

Kaplan-Meier: by surgical margin and no-surgery

Wide/Marginal margin resection of primary lesion group is associated with better survival than no-surgery group



Median overall survival (month, 95%CI)		P<0.05*
Surgery (Wide)	31.0 (25.0-37.0)	
Surgery (Marginal)	25.0 (17.5-32.5)	
Surgery (Intralesional)	11.0 (6.8-15.2)	
No surgery	14.0 (11.0-17.0)	

* Log-rank test

Poster #095 3461335

PATIENT-SPECIFIC CUTTING GUIDES AND 3D-PRINTED TECHNOLOGY FOR PELVIC AND SACRAL TUMOR RESECTION AND COMPLEX ALLOGRAFT RECONSTRUCTION: OUR EXPERIENCE IN THE RESECTION OF PELVIC AND SPINAL SARCOMA OF BONE

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Objective: Wide-margin resection of pelvic tumors is one of the most challenging procedures in musculoskeletal oncology. The complex 3-Dimensional (3D) anatomy, surrounding visceral and neurovascular structures, and typically large tumor size make resection and reconstruction technically demanding. Advancements in 3D technology have led to patient-specific cutting guides that may better achieve negative margins through more accurate and precise cuts. Additionally, this technique may reduce surgical time, help avoid complications, and prove more cost effective than other modalities. However, despite its promise, there is no consensus supporting its routine use in resection of spinal and pelvic tumors. The aims of this study include: 1) Review a single institution's experience and outcomes in utilizing 3D-printed cutting guides and 3D printed implants for resection and reconstruction of spinal and pelvic tumors 2) Perform analysis of pre-operative planning, intra-operative technique, and post-operative management using this technique.

Methods: IRB approval was obtained and a retrospective evaluation of a ten-year consecutive period was performed at our tertiary academic center. Thirteen patients underwent resection for tumors of the pelvis and/or spine utilizing patient-specific 3D-printed technology. For operative planning, software reformatting of CT and MR images (3D Systems VSP® (Virtual Surgical Planning) Orthopaedics) enabled 3D fabrication of patient-specific cutting guides and implants (My3D™ Personalized Solutions, Onkos Surgical, New Jersey, USA). Patient and tumor demographics, perioperative data, complication profiles, and patient outcomes were recorded.

Results: We reviewed the charts of 13 patients. Six (46.2%) had a diagnosis of chondrosarcoma, 3 (23%) of metastatic carcinoma, 2 (15.4%) of locally advanced soft-tissue sarcoma, and 2 (15.4%) of osteosarcoma. The average age (years, mean ± SD) at surgery was 53.3 ± 18.9. 61.5% of tumors were found in the pelvis (ilium, ischium, pubis, proximal femur), 15.4% in the spine, and 23% in both. Seven (53.8%) patients were treated with chemotherapy or radiation prior to surgery. The average surgical duration (minutes, mean, ± SD) was 392.7 ± 189.7, and average intraoperative blood loss (mL, mean ± SD) was 1476.9 ± 2021.5. 3D-printed cutting guides were utilized in 7 (53.8%) cases, 3D implants in 2 (15.4%), and either or both for surgical simulation and demonstration in the remaining 4. Three of 13 cases (23%) had microscopically contaminated margins (2 with 3D cutting guides and 1 without). Of the successful negative margin resections, margins were within 1 mm in 15.4%, 1.1-5 mm in 38.5%, 5.1-10 mm in 7.7%, and ≥ 10 mm in 7.7%, with no differences detected between those in which a guide was employed and those without. There were three deaths (disease-related = 3) in the immediate postoperative period at a mean (range) 4.6 (1-10) weeks, and 1 disease-related death at 53 weeks following surgery. Only 1 patient had a perioperative complication as defined by Clavien-Dindo criteria (blood transfusion, Grade II=1). Of the 10 cases with negative margins, 2 developed local recurrence and 1 developed distant disease. The remaining cases with negative margins were disease-free at maximum follow-up of 233 weeks. Out of the 12 patients whose follow-up was documented, 6 (50%) were alive and disease-free at study conclusion.

Conclusion: Utilizing-3D printed technology such as implants and patient-specific cutting guides, our institution has successfully performed resection of pelvic and spinal sarcomas. This technology can be useful but has not emerged in our clinical practice as a clear determinant of margin status, disease progression, or survival, mostly due to rarity of use. While we believe this technique offers advantages over freehand cutting and navigated surgical techniques during resections of pelvic and spinal tumors, there is no substitute for anatomic understanding and operative experience.

Table 1. Brief Characteristics and Results of 13 Cases of Pelvic and Spinal Reconstruction using 3D Technology

Case	Age (years) / Sex	Diagnosis	Location	Reconstruction	Surgery (mins)	Margins	Follow-up	Status
1	54 F	chondrosarcoma	pelvis	Ilium wing cutting guide	194	Negative	4 years	CDF
2	67 M	MBD	pelvis	Sacral cutting guide	614	Negative	1 week	Dcsd.
3	63 M	osteosarcoma	pelvis, spine	acetabular and sacral cutting guides	643	Negative	97 weeks	LR
4	69 F	chondrosarcoma	pelvis	posterior pelvic cutting guide	271	Positive	4 years	CDF
5	42 F	chondrosarcoma	pelvis, femur	trochanteric cutting guide	144	Negative	4 years	CDF
6	65 F	chondrosarcoma	pelvis	posterior sacral/pelvic cutting guide	642	Positive	4 years	CDF
7	77 F	STS	pelvis, spine	posterior pelvic cutting guide	315	Negative	4 years	CDF
8	32 F	MBD	pelvis	3D-printed metallic hemipelvis implant	597	Negative	4 years	CDF
9	40 F	chondrosarcoma	pelvis	custom printed ice cream cone prosthesis	397	Negative	15 weeks	Mets
10	17 M	osteosarcoma	pelvis	model for visualization only	424	Negative	4 years	CDF
11	70 M	chondrosarcoma	pelvis, spine	model for visualization only	478	Negative	31 weeks 53 weeks	LR Dcsd.
12	30 M	STS	scapula, spine	model for visualization only; thoracic sarcoma	137	Positive	10 weeks	Dcsd.
13	67 M	MBD	spine	Demonstration only; cervical MBD/ corpectomy	249	unspecified	3 weeks	Dcsd.

MBD, metastatic bone disease; STS, soft tissue sarcoma; F, female; M, male; CDF, continuous disease free; LR, local recurrence; Mets, metastatic disease; Dcsd., deceased.

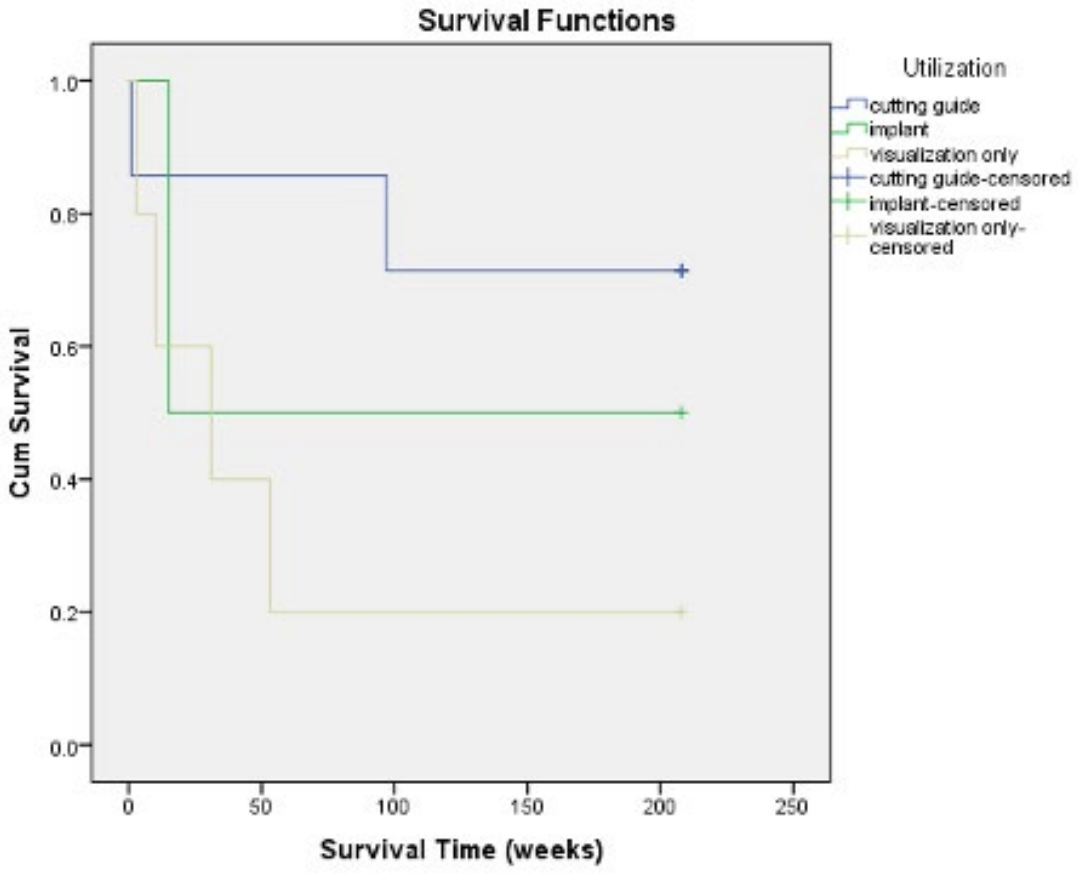

Figure 1. Event-free cumulative-patient survival probabilities by procedure, as estimated from Kaplan and Meier analyses. Events include development of local recurrence, metastatic disease, or death, and were defined as time from surgical procedure to event-related incident. Survivorship plots are representative of procedures using only 3D cutting guides (cutting guide), only 3D implants (implant), or 3D bone models for demonstration (visualization only). p=0.206.

Poster #096 3461337

NON-RANDOM ASSOCIATION OF BREAST IMPLANT SURGERY AND DESMOID TUMOR FORMATION

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Objective: Several studies suggest that breast augmentation surgery with implants is a risk factor for the development of breast desmoid tumors (BD). Whether this correlation truly exists is still unknown, as the evidence is limited to anecdotal reports. Herein, we present the largest case series to be published. Our aim is to analyze the clinical characteristics, treatments, and outcomes of patients who developed BD after the placement of a breast implant.

Methods: Patients with BD and a history of breast augmentation with implants seen at a single academic medical center between 2000-2020 were identified via radiology, breast, and sarcoma databases. Clinical data were extracted from patient records. The standardized incidence ratio (SIR) was calculated to assess the correlation between BD and breast augmentation with implants. The identified cases were pooled with literature cases for descriptive and statistical analyses. Progression free survival curves were estimated using the Kaplan-Meier method and Cox proportional-hazards modeling was used to estimate the hazard ratios for different factors that could influence recurrence risk.

Results: 12 patients from our institution and an additional 58 cases in the literature were identified. All patients were female and the mean age at diagnosis was 38 years old (range 21-66). The mean time from implant placement to diagnosis was 2.9 years (range 0.3 – 12). Regarding treatment of the BD, 66 patients (74%) underwent surgical resection, 8 (9%) received cytotoxic chemotherapy, 3 (3%) received sorafenib, 8 (9%) received tamoxifen, and 4 (5%) either received non-steroidal anti-inflammatories or underwent surveillance. After surgical resection, the 2-year recurrence free survival rate was 68% (95% CI 55–81%). The risk of recurrence was significantly lower for an R0 resection compared to an R1 or R2 resection (HR 0.12; 95% CI 0.023-0.61; P<0.05). There was no statistically significant difference between the risk of progression in surgical patients who underwent implant removal and those who had implants replaced. The calculated SIR was 440 (95% CI 224-738) to 750 (95% CI 379-1245), suggesting a 440 to 750 times higher risk of encountering BD after breast augmentation with implants in comparison to the risk of BD in the general population.

Conclusion: We present a statistically significant nonrandom association between breast augmentation with implants and the development of BD. Whether BD arise from the surgical trauma itself or from the biomaterial of the implants is unknown. Due to the high recurrence rate seen after an R1 or R2 resection, surgery should be performed only if an R0 resection is attainable. This association may be considered for inclusion in the informed consent for breast augmentation surgery with implants and warrants further investigation regarding the precise biological mechanism.

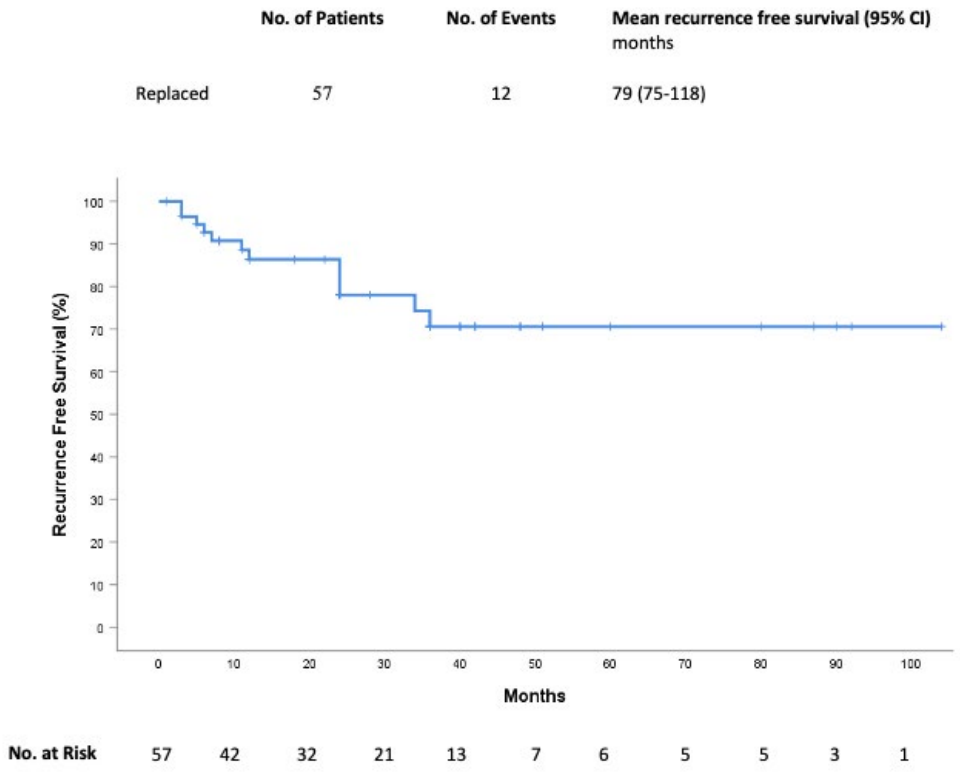
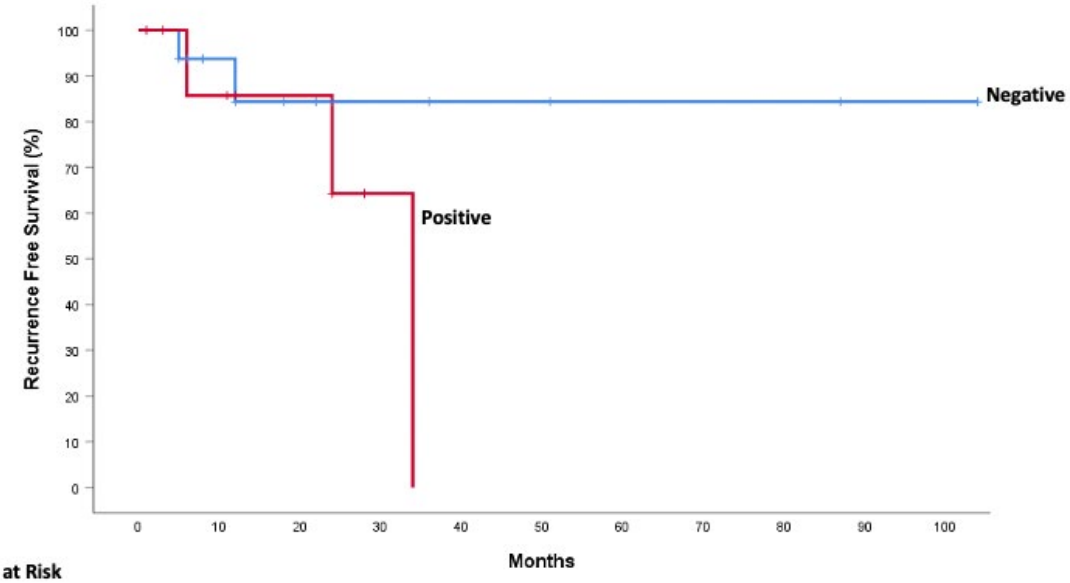


Figure 1. Kaplan–Meier Estimates of the Recurrence-free Survival after Surgery.

Figure 2. Kaplan–Meier Estimates of the Recurrence-free Survival by Surgical Margins.

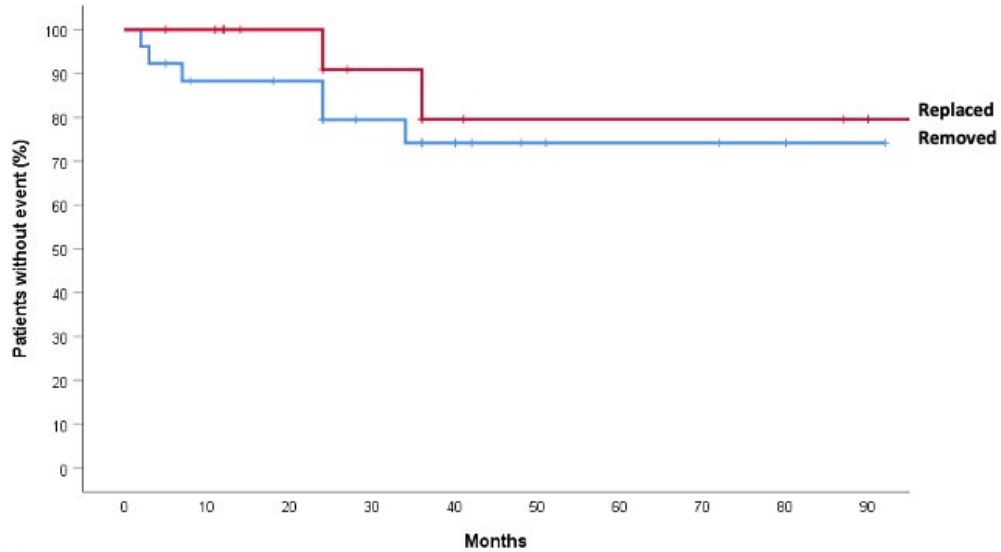
	No. of Patients	No. of Events	Mean progression free survival (95% CI) months
Negative	16	2	89 (69-108)
Positive	9	3	27 (18-37)



No. at Risk											
Negative	16	10	7	5	3	3	2	2	2	1	1
Positive	9	6	4	1	0	0	0	0	0	0	0

Figure 3. Kaplan–Meier Estimates of the Duration of Progression-free Survival by Implant Management Strategy.

	No. of Patients	No. of Events	Mean progression free survival (95% CI) months
Replaced	17	2	96 (75-118)
Removed	26	6	72 (79-105)



No. at Risk										
Replaced	17	16	11	8	5	4	4	4	4	3
Removed	26	21	20	15	10	4	3	3	2	1

Poster #097 3461438

A PHASE 1B/3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF TAZEMETOSTAT PLUS DOXORUBICIN AS FRONTLINE THERAPY FOR PATIENTS WITH ADVANCED EPITHELIOID SARCOMA

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Objective: Epithelioid sarcoma (ES) is characterized by loss of inhibitor of integrase 1 (INI1), allowing enhancer of zeste homologue 2 (EZH2) to repress cell differentiation and promote tumorigenesis. Tazemetostat is an EZH2 inhibitor approved by the FDA as monotherapy for the treatment of patients aged ≥16 years with metastatic or locally advanced ES ineligible for complete resection. The most common (>20%) adverse events include pain, fatigue, nausea, decreased appetite, vomiting, and constipation. Tazemetostat demonstrated anti-cancer activity in patients with ES who previously received doxorubicin, a commonly used front-line, FDA-approved therapy for soft tissue sarcomas (STS), including ES. Preclinical studies have demonstrated synergy between tazemetostat and doxorubicin. This phase 1b/3 study (NCT04204941) is assessing the safety and efficacy of tazemetostat + doxorubicin in patients with advanced ES.

Methods: This study is enrolling treatment-naïve adult patients with histologically confirmed STS (phase 1b) or patients with INI1-deficient ES (phase 3) with an ECOG performance status of 0–2 and life expectancy of ≥3 months. The open-label phase 1b portion is currently enrolling up to 24 patients with STS. The primary objectives are to evaluate the safety and tolerability of tazemetostat + doxorubicin and to identify the recommended phase 3 dose (RP3D). Using a standard 3 + 3 design, tazemetostat will be evaluated at 3 dose levels (400 mg, 600 mg, and 800 mg orally twice daily) with a standard fixed-dose of doxorubicin (75 mg/m^2 on day 1 of 21-day cycles for up to 6 cycles). After completion of doxorubicin, patients will continue to receive tazemetostat monotherapy until disease progression or intolerable toxicity. Up to 12 additional patients will be enrolled at the maximum tolerated dose for collection of additional safety and pharmacokinetic (PK) data.

The double-blind phase 3 study will randomize (1:1) up to 140 patients to receive either tazemetostat (RP3D) + doxorubicin (75 mg/m^2) or placebo + doxorubicin. The adaptive study design will allow sample size re-estimation (at interim analysis) to up to 200 patients. Patients may continue tazemetostat or placebo monotherapy after completing 6 cycles of tazemetostat + doxorubicin. Tumor assessments will be performed at screening and every 6 weeks from the start of dosing. The primary objective of phase 3 will be to evaluate progression-free survival (PFS) by independent review committee. Secondary objectives will include investigator-assessed PFS, overall survival, safety, disease control rate, overall response rate, duration of response, time to subsequent anticancer therapy, PFS on next treatment, quality of life, and PK.

Results: N/A

Conclusion: N/A

Poster #098 3461452

OUTCOMES OF EWING SARCOMA/ EWING'S-LIKE SARCOMA (ES) IN PATIENTS AGED OVER 25

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Objective: To describe the management and outcomes of patients aged over 25 with ES in a tertiary referral centre.

Methods: All patients with ES treated at our centre between January 2012 and December 2019 were included. All underwent pathological review and were managed within a tertiary sarcoma MDT. Data was collected and median overall (OS) survival and progression free (PFS) survival were estimated with Kaplan Meier methodology using PRISM software.

Results: 17 patients were included. 15/17 patient's histology showed ES with positive translocations for EWSR1-FL1/ EWSR1-ERG. 2 had a Ewing's like small round blue cell tumour with negative translocation.

Systemic treatment
All patients received chemotherapy (CT), 16 were commenced on VIDE/VAI (Vincristine, Ifosfamide, Doxorubicin, Etoposide, Actinomycin D and cyclophosphamide), 1 had reduced performance status and was commenced on doxorubicin and ifosfamide. 13/17 were evaluated for treatment response with repeat imaging after 4 cycles (4 cases had no measurable disease due to prior excision): 1 had complete response, 11 had partial response and 2 had stable disease.

Local treatment
9 patients had excision surgery (limb-sparing-3, re-excision-2). Pathological review demonstrated: 100% necrosis in 2, <95% response in 5 (1patient-10%, 4 patients ≥60%), and was not described in 2 cases (1 due to piecemeal excision, 1 described as some viable tumour). Five showed clear margins. 4 had close/involved margins.

13 received radiotherapy (RT); 5 received RT alone and 8 received RT with surgery (pre-operative 3 and post-operative 5). The preoperative dose was 50.4Gy in 28 fractions, and the post-operative dose was 54Gy in 30 fractions except for 1 patient who had 30Gy in 20 fractions to the abdomen.

Toxicity
CT related: febrile neutropaenia, thrombocytopaenia and mucositis. ovarian failure (2 cases) and ifosfamide encephalopathy necessitating change to cyclophosphamide (2 patients).
RT related: Patients with Grade 1-2 skin reaction (4), skin fibrosis (1), dyspepsia (1), mucositis (2) and insufficiency fractures (2)

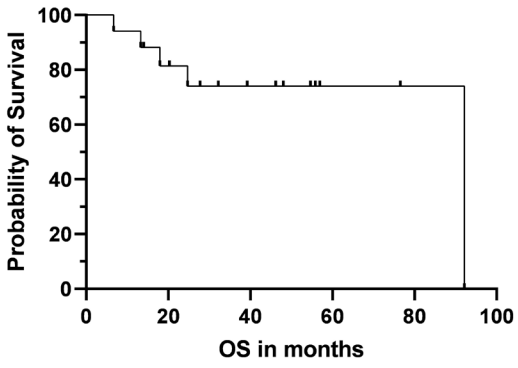
Follow Up and Disease progression
The median follow up for all patients was 31 months (range 13 -90)**.** 7 patients had disease progression/recurrence. Median time to progression was 12 months (range 5-34).
In metastatic disease patients (MD), 2 progressed in their metastatic lesion and 1 in both local and metastatic disease. 1 had palliative RT, others declined treatment and these patients died within 1 year of progression.
Of 4 patients with localised disease (LD), 1 had local progression and 3 relapsed with distant metastases. 1 patient had a single lung recurrence which was treated with stereotactic ablative body radiation (SABR) with volumetric modulated arc therapy (VMAT) 55Gy in 5 fractions. 3 months later, the patient had new pulmonary lesions waiting for surgical opinion. 3 were treated in the rEECur trial, 1 completed 6 cycles of topotecan and cyclophosphamide (TC) and is being followed up. Another progressed after 2 cycles of docetaxel and gemcitabine and received 3rd line CT with irinotecan and temozolamide (IT). Later, the patient underwent palliative RT to lung and bone metastases but died 13 months after progression. Third patient received IT, subsequently progressed, and received TC, oral etoposide and carboplatin. The patient also had palliative RT to the lung and died 45 months after initial relapse.

Survival: 12 patients remain alive and 5 (2 LD and 3 MD) have died. OS for LD was 90 months and for MD was 19 months. The OS for all patients was 32 months.

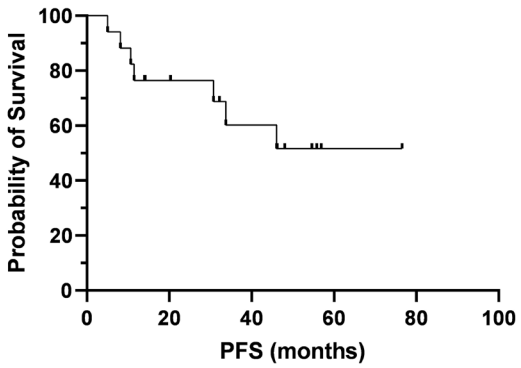
Conclusion: All patients with localised disease were treated with the European standard of VIDE/VAI. The PFS and OS seen in these patients reflects that described in the literature. This data supports the use of intensive regimes in patients with ES in sarcoma treatment centres. Patients with metastatic disease have a poor prognosis. Treatments are being currently evaluated for these patients in the rEECur trial and more work is needed to improve outcomes.

Characteristics for adults with Ewing's sarcoma (N=17)

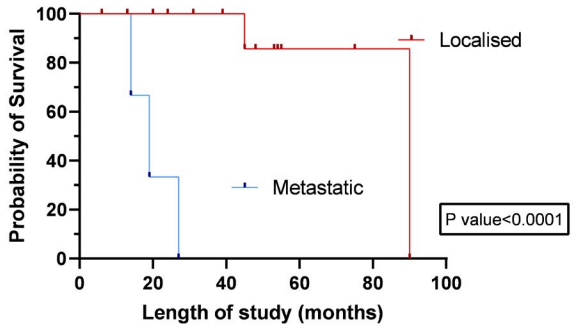
Characteristics	Localised	Metastatic	All patients
Number of patients	14	3	17
Gender			
Men	9	1	10
Women	5	2	7
Median age	31.5 years (range 26-48)	48 years (32-52)	33 years
Primary tumour tissue of origin			
Bone	5	0	5
Extra osseous	9	3	12
Location			
Peripheral	4	2	6
Central/Axial	10	1	11
Size			
<8cm	5	2	7
>8cm	8	1	9
Unavailable	1	0	1
Chemotherapy			
VIDE/VAI	14	2	16
Doxorubicin/ifosfamide	0	1	1
Local treatment			
Surgery	1	0	1
Surgery and Radiotherapy	8	0	8
Radiotherapy	4	1	5
Chemotherapy alone	1	2	3
Local Progression	1	3	4
Distant relapse	3	0	3



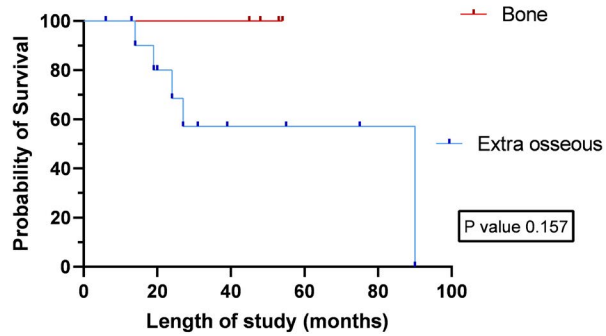
Overall survival rate for all patients with ES (n=17)



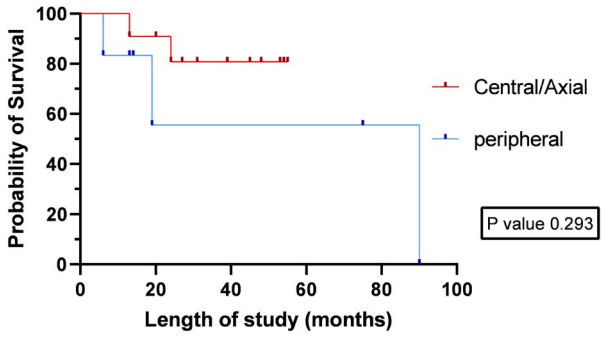
Progression free survival rate for all patients with ES



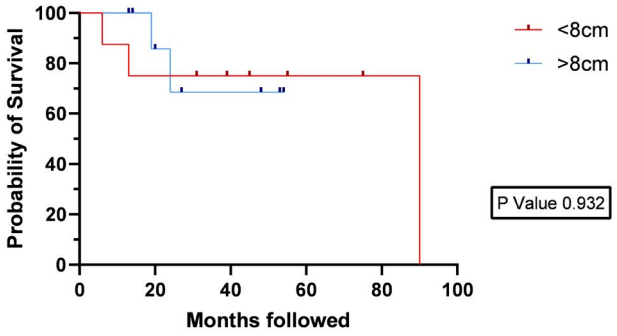
Overall survival rates for patients with localised (n=14) and metastatic (n=3) ES



Overall survival rates for patients with primary origin in bone (n=5) and extraosseous (n=12) ES



Overall survival rates for patients with central (n=11) and peripheral (n=6) primary ES



Overall survival rates for patients with primary tumour size <8cm(n=8) and >8cm (n=9)

Poster #099 3461465

GRADE OF PRIMARY CUTANEOUS LEIOMYOSARCOMA DICTATES CLINICAL OUTCOME RISK

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Objective: Primary cutaneous leiomyosarcoma (cLMS) arises in the dermis and has been reported to exhibit an indolent course of disease with extremely low risk of recurrence and close to 100% disease free survival. Deneve et. al. (*Cancer Control*, 2013) previously reported on 33 patients from this institution with cLMS, noting no locoregional recurrence, distant metastasis, or deaths during the observed treatment period. Here we report an update on the clinical, pathologic and treatment characteristics of this rare tumor as well as oncologic outcomes, including updated rates of recurrence and survival in a larger series of cLMS patients with longer follow up treated at a single institution.

Methods: All patients that underwent resection of primary cLMS between 2006-2019 were included. Chart review abstracted data regarding diagnosis, treatment, surveillance, and pattern of recurrence. Data analysis included descriptive statistics of outcome measures.

Results: Eighty-eight patients with cLMS were evaluated. The majority were men (n=68, 77%) and Caucasian (n=85, 97%), with median age at diagnosis of 66 years (range 20-96). 65% of tumors were located on the extremities (upper: n=22, 25%; lower: n=35, 40%), with median clinical size of 1.3 cm (range 0.3-15 cm). Sixty (68%) patients received preoperative staging imaging of the chest with PET (n=5, 6%), CT (n=37, 42%), MRI (n=2, 2%) or plain film radiography (n=15, 17%), none of which demonstrated distant metastasis. (Table 1)

Pathologic assessment revealed the following breakdown into low (n=42, 48%), intermediate (n=28, 32%) and high (n=18, 20%) grade lesions. Most tumors demonstrated low mitotic activity (n=64, 73%), with immunohistochemistry positive for smooth muscle actin (n=70, 80%) while negative for S-100 (n=58, 66%). Pre-operative biopsy was discordant with post-operative final pathology in 6 (7%) of cases, of which 5 increased while 1 decreased in grade severity. For the purposes of analysis, higher grade was chosen for classification. A significant proportion demonstrated extension from the dermis into subcutaneous tissue (n=36, 41%) and a much smaller proportion extending further into muscle (n=3, 3%).
(Table 1)

All 88 patients underwent surgical resection as primary treatment with a median of 1 cm radical margins (range 0.5-2 cm). Seven patients received adjuvant radiation to the primary site with median dose of 62 Gy (range 60-66 Gy). No patients received adjuvant chemotherapy. Over a median follow-up of 27.5 months (range 1-131 months), recurrences were identified in 9 patients (10%; local, n=3; local and regional, n=1; local and distant, n=2; distant, n=3). Overall median time to recurrence was 24 months (range 7-82 months). Median time to local recurrence was 16 months (range 7-82 months), while median time to distant recurrence was 34 months (range 14-62 months). No patient with low grade tumor experienced recurrence, all recurrent patients (9/9, 100%) were classified as moderate to high grade tumors. Of those who recurred, median clinical tumor size was 2 cm (range 0.3-4 cm), were distributed across all margins of resection, and were evenly divided between the extremity (n=3), trunk (n=3) and head/neck (n=3). Eight (89%) of these patients had tumors that extended into or beyond the subcutaneous tissue on primary resection. Seven (78%) had resection at or deeper than the level of underlying fascia. Four (4.5%) died of disease. (Table 1)

Conclusion: Excellent local control with an almost 90% local recurrence free survival was seen in this large cohort, with no low-grade patients experiencing a recurrence. Long-term outcomes with a disease specific survival of over 95% were observed with primary surgical resection as the sole therapeutic modality in most cases of cLMS. For patients with intermediate to high grade disease, there is a small, but significant potential of recurrence and metastasis and therefore extended clinical surveillance following treatment is encouraged.

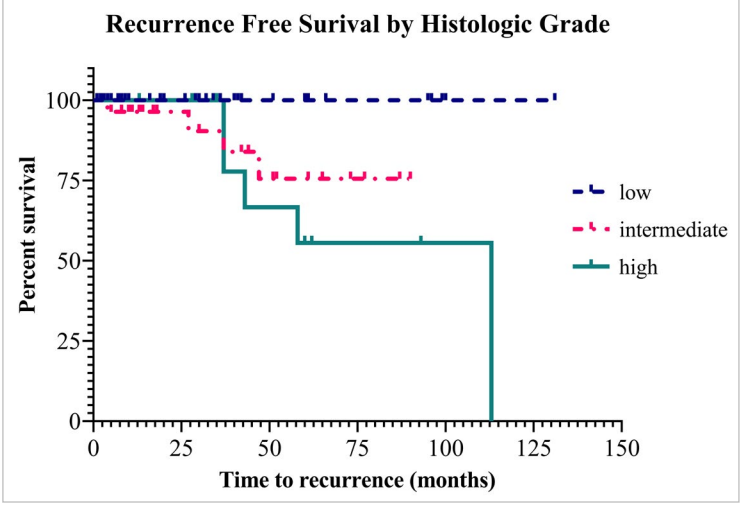
Patient Characteristics, Treatment and Outcomes

Clinical Characteristics	
Caucasian Median age at diagnosis	85 (97%) 66 years (range 20-96)
Gender Men Women	 68 (77%) 20 (23%)
Immunocompromised status	5 (6%)
Tumor location Head/neck Trunk Upper extremity Lower extremity	 13 (15%) 18 (20%) 22 (25%) 35 (40%)
Clinical tumor size < 1 cm 1 – 1.9 cm 2 – 4 cm > 4 cm	 19 (22%) 42 (48%) 19 (22%) 6 (7%)
Pre-operative imaging None Chest X-Ray CT, PET, or MRI	 35 (40%) 13 (15%) 40 (45%)
Histologic Characteristics	
Pathologic tumor size No residual tumor < 1 cm 1 – 1.9 cm 2 – 4 cm > 4 cm	 30 (34%) 23 (26%) 17 (19%) 16 (18%) 2 (2%)
Tumor grade Low Intermediate High	 42 (48%) 28 (32%) 18 (20%)
Depth of invasion Dermis Subcutaneous tissue Muscle	 49 (56%) 36 (41%) 3 (3%)

Treatment and Outcomes	
Operative margin 0.5 cm 1 cm 1.5 cm 2 cm Unknown	 1 (1%) 59 (67%) 9 (10%) 10 (11%) 9 (10%)
Re-excision for positive margin	6 (7%)
Complication None Wound infection Wound breakdown	 82 (93%) 4 (5%) 2 (2%)
Adjuvant treatment None Radiation Chemotherapy	 81 (92%) 7 (8%) 0
Recurrence None Yes	 79 (90%) 9 (10%)
Recurrence location Local Local and regional Local and distant Distant	 3 1 2 3
Median time to recurrence Local Distant	24 months (range 7 – 82) 16 months (range 7 – 82) 34 months (range 14 – 62)
Follow-up status No evidence of disease Alive with disease Dead of disease Dead of other cause Dead of unknown cause	 77 (88%) 1 (1%) 4 (5%) 5 (6%) 1 (1%)

*HPF: high powered field

Figure 1.



Poster #100 3461487

OXYGEN TENSION AND MACROPHAGES MEDIATE PROLIFERATION OF OSTEOSARCOMA CELLS IN 3-DIMENSIONAL CULTURE

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Objective: Current *in vitro* and *in vivo* models have failed to accurately mimic the Osteosarcoma (OS) metastatic process and lack efficient throughput for pharmacologic testing. There is new enthusiasm with the development of 3D *in vitro* sarcoma models. These models may better recapitulate the tumor microenvironment with tumor cell heterogeneity, histologic architecture, cell-extracellular matrix interactions, and niche conditions like hypoxia, pH, and local cytokines. For example, hypoxia has been linked to increases in matrix metalloproteinases (MMPs) which degrade basement membranes and enable cell migration. Current approaches to interrogate key signaling pathways in OS are pursued in monolayer culture using homotypic cell populations, each of which lacks clinical relevance and represents a likely stumbling block in effectively discovering druggable targets to inhibit metastasis. Since current models are insufficient to model this cancer, we hypothesized that OS would exhibit differences in MMP production, metabolic activity, and proliferation as a function of local oxygen concentration when entrapped in a clinically relevant engineered hydrogel.

Methods: A homotypic culture of highly metastatic murine K7M2 osteosarcoma cells (HOM) or a heterotypic culture of K7M2 and RAW 264.7 murine macrophages (HET) at an 85:15 ratio were entrapped in fibrin-alginate interpenetrating network (IPN) hydrogels at $3x10^6$ cells/mL. IPNs were formed from 3% w/v MVG sodium alginate, 2.5 µL/mL thrombin, 20 mg/mL fibrinogen, and crosslinked in 10 mM $CaCl_2$ solution. These IPNs provide native adhesion motifs from fibrinogen, controlled stiffness from alginate, and possess a shear storage modulus of 1 kPa, which is similar to native bone marrow. Gels were cultured in complete media for up to 7 days in 5% or 21% oxygen (O_2). We measured the diameter of gels with ImageJ, cell proliferation by DNA content, and metabolic activity by MTT. To investigate the effect of MMP activity on cell proliferation, we cultured some gels in the presence of GM6001 (25 µM), a broad-spectrum inhibitor of MMP activity. Data are presented as mean ± SD with a minimum of n=4 per group per time point.

Results: There were no significant differences in IPN hydrogel diameter after 7 days of culture in either of the oxygen tensions tested. Cell proliferation was inversely correlated with oxygen tension after 7 days in culture. In the absence of GM6001, DNA content in HOM gels maintained in 5% oxygen (1246.0 ± 102.9 ng) for 7 days was significantly greater than gels maintained in ambient air (691.9 ± 302.5 ng; $p<0.05$, n=4). We observed similar trends in proliferation as a function of oxygen tension with heterotypic (HET) cultures. Importantly, DNA content was significantly greater in HET gels compared to HOM gels ($p<0.001$, n=4) after 7 days at both 5% and 21% oxygen. DNA content in HET gels maintained in 5% oxygen (1715.7 ± 28.3 ng) for 7 days was significantly greater than gels maintained in ambient air (991.9 ± 16.5 ng; $p<0.0001$, n=4). Cell proliferation was not significantly affected by abrogation of MMP activity with a soluble inhibitor in HOM or HET gels at either oxygen tension.

Conclusion: These data demonstrate that oxygen tension has a significant effect on K7M2 proliferation within a biomimetic 3-dimensional platform, suggesting this is a key parameter for consideration in such studies. Unlike many mammalian cells that proliferate faster in ambient air, K7M2 cells in these IPNs proliferated 2-3 times faster in bone physiologic oxygen tensions compared to ambient air. Our data also demonstrate that the addition of macrophages to K7M2s in culture can enhance proliferation within this gel. Additionally, the apparent lack of efficacy of MMP inhibition indicates that either MMP activity is not critical for K7M2 proliferation or the quantity of material vulnerable to MMP-mediated degradation in these IPNs is too small to influence proliferation. Additional studies are necessary to describe this phenomenon.

Figure 1. Fibrin-alginate IPN morphology. (Top) IPNs immediately upon entrapment of cells. Scale bar represents 1 cm. (Bottom) Gross morphological view of IPN containing K7M2s (HOM) at 21% O_2 after 7 days in culture.

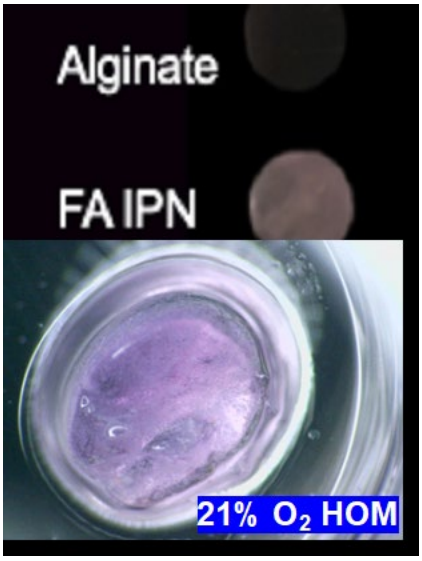
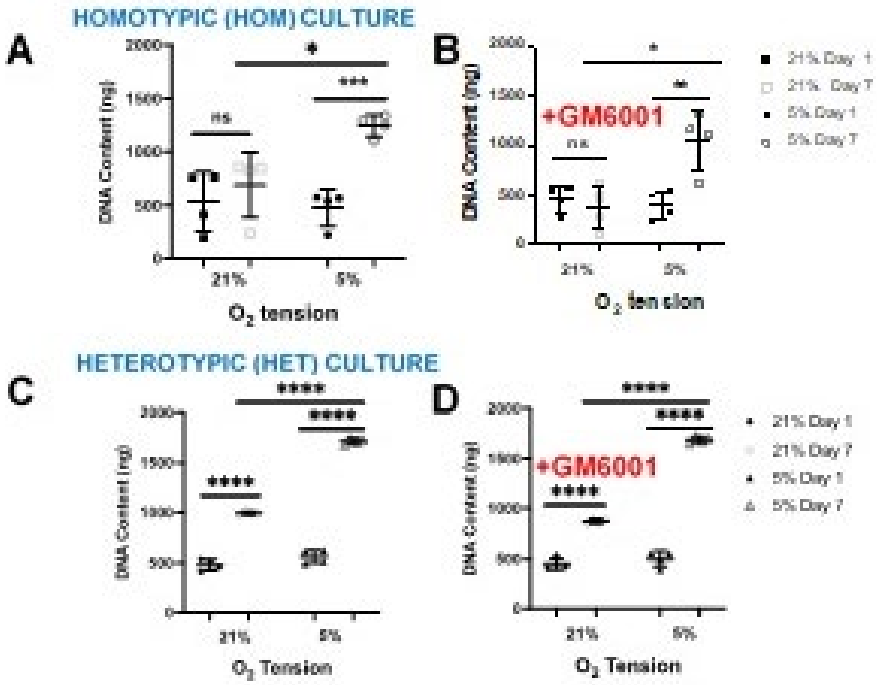


Figure 2. Cell proliferation is dependent upon oxygen tension and presence of macrophages as accessory cells. DNA content, as an indicator of cell number within homotypic cultures (K7M2 cells) over 7 days (A) or (B) in the presence of GM6001 (n=4 per group, *p<0.05 vs. 1% O2; **p<0.01; ***p<0.001). DNA content within heterotypic cultures of K7M2 cells and RAW 264.7 macrophages over 7 days (C) or (D) in the presence of GM6001 (n=4 per group, ****p<0.0001). Data are mean ± standard deviation.



Poster #101 3461493

PATIENT-SPECIFIC CUTTING GUIDES AND 3D-PRINTED TECHNOLOGY FOR INTERCALARY LONG BONE RESECTION AND ALLOGRAFT RECONSTRUCTION: OUR EXPERIENCE IN THE RESECTION OF EXTREMITY SARCOMA OF BONE

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Objective: In sarcoma surgery, margin status is a known predictor of disease-related outcomes. Additionally, surgical and functional outcomes are dependent on remaining bone stock. Advancements in three-dimensional (3D) printing technology have led to patient-specific cutting guides that may better achieve negative margins through more accurate and precise cuts, thus preserving bone stock. Additionally, this technique may affect surgical time, allograft union rates, and the perioperative complication profile. While recent studies suggest 3D-printed technologies offer a cost-effective means of improving the procedure compared to free-hand and navigational techniques, there is little support for its consensus recommendation in resection of extremity sarcoma. The aims of this study include: 1) Review of a single institution's experience and outcomes utilizing 3D-printed cutting guides for resection of extremity sarcoma of long-bones with intercalary allograft reconstruction. 2) Analysis of pre-operative planning, intra-operative technique, and post-operative management of this procedure.

Methods: Six patients underwent limb-salvage surgery for sarcoma of a long-bone, utilizing both a patient-specific 3D-printed cutting guide and an intercalary allograft for reconstruction. IRB approval was obtained and a retrospective evaluation recorded disease-related, surgical, and functional outcomes for each case. For operative planning, software reformatting of CT and MR images (3D Systems VSP® (Virtual Surgical Planning) Orthopaedics) enabled 3D fabrication of patient-specific cutting guides and implants (My3D™ Personalized Solutions, Onkos Surgical, New Jersey, USA) (Figures 1-3). We describe 6 cases of malignant bone tumors in patients who underwent successful limb-salvage surgery using this 3D-printed technology.

Results: Two (33.3%) patients had a diagnosis of osteosarcoma, 1 (16.7%) of chondrosarcoma, and 3 (50.0%) of Ewing's sarcoma. The average age (mean ± SD) at surgery was 30.8 ± 15.9 years. Three (50.0%) tumors were in the femur and 3 (50.0%) were in the tibia. Three (50.0%) patients were treated with chemotherapy therapy prior to surgery, and no patients had presurgical radiation. One patient was treated at an outside facility with an incomplete previous resection. The average surgical duration (mean ± SD) was 324.8 ± 162.3 minutes, and average intraoperative blood loss (mean ± SD) was 483.3 ± 385.6 mL. Each of the 6 (100%) cases recorded negative margins, and the average follow-up time (mean ± SD) after surgery was 102.8 ± 83.6 weeks. The average time (mean ± SD) to bony union defined radiographically as the earliest identifiable per-osteotomy site union was 23.0 ± 9.5 weeks. Seven of 10 (70%) cumulative (proximal and distal) osteotomy sites went onto union, with an overall nonunion rate of 30% defined as the need for surgery to achieve per-osteotomy site union. Of the cumulative nonunion patients, 2 (66.7%) received postoperative chemotherapy and/or radiation. Five (83.3%) patients had graft retention at their most recent follow-up, which varied among patients. Long-term complications interpreted by modified Henderson classification were limited to 2 (33.3%) overall patients (Type 3; implant failure=2). Finally, there were 0 local recurrences and 1 (16.7%) incidence of resultant metastasis by maximum recorded follow-up of 4.5 years (Table 1).

Conclusion: Utilizing 3D-printed technology and patient-specific cutting guides, our institution has been able to successfully perform limb salvage surgery. Our study demonstrates a successful negative margin resection in each of the 6 cases: ≤ 1 mm (33.3%); 1.1-3 mm (33.3%); 3.1-5 mm (16.7%); and ≥ 5.1 mm (16.7%). Cumulative bony union was achieved in 70% of cases, with a relatively low short to midterm complication rate of 33.3% according to modified Henderson criteria. This novel technique, we believe, offers advantages both to freehand cuts and navigated techniques during resection of extremity sarcoma of bone.

Brief Characteristics and Postoperative Results of 6 Cases

Case	Age/ Sex	Site	Margins	Surgery (min)	Union (weeks)	Revision (Yes/No)	Graft retention (Yes/No)	Therapy	Complication	Status	Follow-up (weeks)	Diagnosis
1	32 F	Tibia	Negative (1mm)	260	P (24)	Y	N	none	HF	CDF	205	Osteo-sarcoma
2	18 M	Tibia	Negative (1mm)	396	P (30)	Y	N	AC/AR	HF	CDF	191	Ewing's sarcoma
3	60 F	Femur	Negative (2mm)	171	D (9)	N	Y	AC	none	CDF	102	Ewing's sarcoma
4	21 M	Tibia	Negative (3mm)	248	B (33)	N	Y	AC/AR	none	Mets	95	Osteo-sarcoma
5	35 F	Femur	Negative (6mm)	253	B (19)	N	Y	none	none	CDF	21	Chondro-sarcoma
6	19 M	Femur	Negative (4mm)	621	-	-	-	-	none	CDF	3	Ewing's sarcoma

P, proximal junction bony union; D, distal junction bony union; B, both proximal and distal junction bony union; HF, hardware failure; Mets, metastatic disease after surgery; CDF, continued disease-free; AC, adjuvant chemotherapy; AR, adjuvant radiation therapy; M, male; F, female.

Figure 1. 3D instrumentation design, along with allograft holder.

Figure 2. Partnership with tissue bank for digitally scanned allograft match.

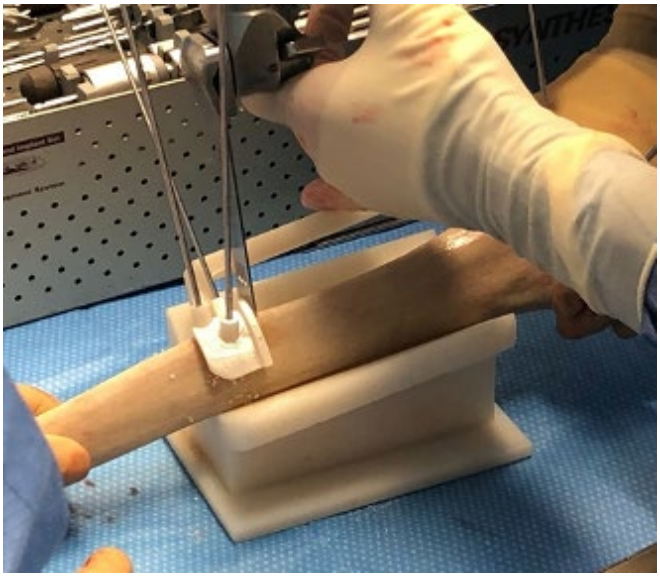
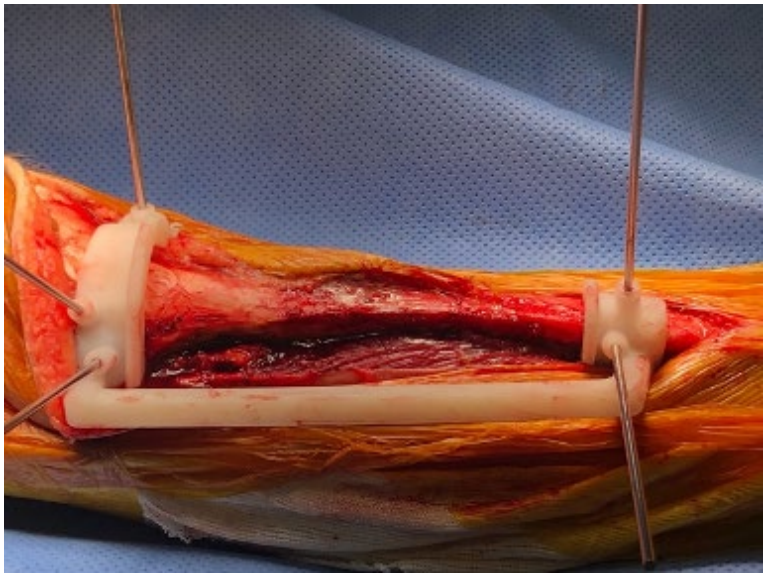


Figure 3. Intraoperative allograft matching using 3D-printed patient specific cutting guide.



Poster #102 3461507

SHORTCOMINGS OF FUNCTIONAL IMAGING: FAILURE OF MIBG SCAN TO DETECT A BENIGN TRANSFORMATION OF SOFT-TISSUE MALIGNANCY IN THREE CHILDREN

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Objective: ^{123}*I-Meta*-iodobenzylguanidine (MIBG) scans are used to detect neuroendocrine tumors based on the production of catecholamines. They are typically used to diagnosis paragangliomas, pheochromocytomas, ganglioneuromas (GL), and neuroblastoma (NBL) (Decarolis, et al, BMC Cancer 2016). For the most aggressive of these, NBL, MIBG scanning is used prognostically. In the current International Neuroblastoma Response Criteria (INRC) guidelines from 2017, MIBG and anatomic imaging are be used to assess tumor response and next steps in treatment. MIBG positivity is interpreted as treatment failure and incurable refractory disease. We describe 3 cases of childhood NBL where MIBG was strongly avid after intense chemotherapy. In 2 of the 3, tissue biopsy showed transformation of NBL to GL a benign tumor. In the third, the patient was on hospice, thriving, for 5 years before a biopsy of the MIBG positive bone metastasis was proven to also be a benign GL (Brodeur, Cell Tissue Res 2018). Since GL can occasionally be MIBG positive and NBL can occasionally differentiate into GL, we recommend a change to the current international recommendations to include a mandatory biopsy of MIBG positive lesions before assuming the patient is incurable.

Methods: A literature review on PubMed and Google Scholar with search terms: "neuroblastoma", "ganglioneuroblastoma", "MIBG false positive", and "MIBG neuroblastoma false positive" in conjunction with a review of patient records.

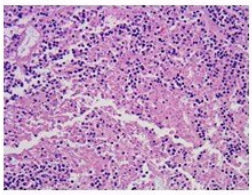
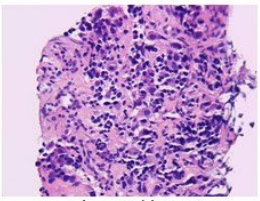
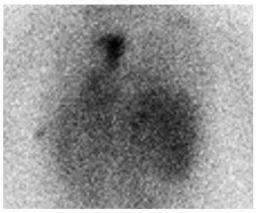
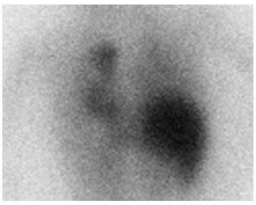
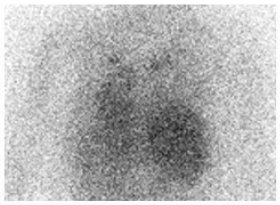
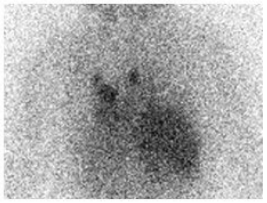
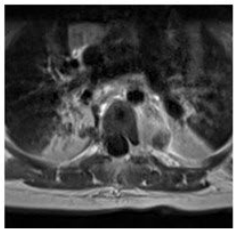
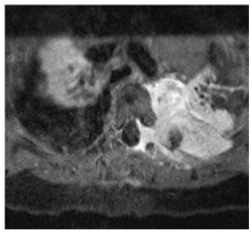
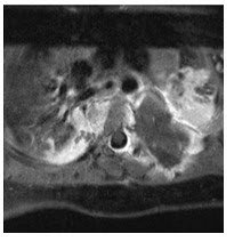
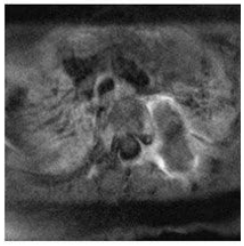
Results: All three patients' biopsies showed their NBL had differentiated into GL. Patient 3, unfortunately, received palliative radiation to the MIBG avid lesion, and then put on hospice and 5 years later developed a radiation-induced osteosarcoma (OST) in his femur. The patients have all been in remission from NBL, alive with excellent QoL now for 5.1, 3.1, and 5.0 years respectively.

Conclusion: Several studies have found low incidence of false positives in MIBG scans, ranging from 1-5% (Bleeker, et al, Cochrane Database Syst Rev 2015). Because of this low incidence, the INRC and the Children's Oncology Group protocols do not require biopsy confirmation of MIBG avid lesions as proof of presumptive treatment failure or relapse. This may cause a small subset of patients' treatment to be halted, or children to be unnecessarily treated (such as radiation in the patient that developed OST) or be placed on a non-curative palliative paradigm. When MIBG scans make it appear as though no progress in being made in a patient's treatment, we recommend a biopsy for confirmation.

TABLE:

Patient	Age (years)	Diagnosis	Treatment	Post-Treatment	Biopsy (Y/N)
1	2	intermediate risk, stage 3, paraspinal NBL	4 cycles of intensive chemotherapy	consistent increase in MIBG uptake and size	Y
2	16	very high risk, stage 4 NBL	6 cycles of intensive chemotherapy, radiation and immunotherapy	no change in size and an increased MIBG uptake	Y
3	10	very high risk, stage 4 NBL	8 cycles of intensive chemotherapy, surgery and two stem cell transplants	new MIBG positive bone lesions	Y, after 5 years on hospice with no clinical symptoms

Imaging of Paraspinal neuroblastoma

	Initial	8 months	20 months	23 months
	 neuroblastoma			 ganglioneuroblastoma
MIGB images, Posterior View	 uptake in the left region	 persistent uptake	 decreased uptake in the left region, increased uptake in the	 Increased uptake on both sides
Postcontrast MRIs, Axial View	 Post-surgery: residual tumor seen in the left region	 Mild progression	 new tumor in seen the right region	 decreased size of left tumor
Patient 1				

Poster #103 3461555

SELINEXOR IS MORE ACTIVE THAN DOXORUBICIN IN PATIENT-DERIVED XENOGRAFTS OF DEDIFFERENTIATED LIPOSARCOMA

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Objective: Dedifferentiated liposarcoma (DDLPS) expresses amplified MDM2 with wild-type p53. MDM2 ubiquination of p53 facilitates its XPO1-mediated nuclear export, thus limiting p53 tumor suppressor functions. Consequently, nuclear export is a rational target in DDLPS. Indeed, the first-in-class XPO1 inhibitor selinexor has shown activity in established cell line-based preclinical models of DDLPS and is currently under investigation in a phase III trial versus placebo in advanced DDLPS patients. We directly compared the antitumor activity of selinexor and doxorubicin, the standard front-line medical therapy in sarcomas, on in-house developed patient-derived DDLPS preclinical models.

Methods: This study was carried out on 3 PDX models established from the dedifferentiated component of primary, MDM2-amplified retroperitoneal DDLPS with myogenic (LS-BZ-1), rhabdomyoblastic (LS-GD-1) and epithelioid (LS-BP-1) differentiation, which were histologically and molecularly characterized for their consistency with the originating clinical tumors. Selinexor and doxorubicin were administered as single agents at the reported optimal doses for mouse models when mean tumor volume (TV) was about 100 mm^3, and drug activity was assessed as TV inhibition percentage (TVI%). The effects of drugs were also assessed on two cell lines established from PDXs LS-BZ-1 and LS-GD-1. Western blots were carried out on tumors obtained from untreated and drug-treated mice as well as on cell lines to assess the induction of apoptotic response and the occurrence of variations in the expression and sub-cellular localization of selinexor target proteins (XPO1, p53 and survivin).

Results: All PDX models were marked by amplification of MDM2, CDK4 and HMGA2 genes, although to a variable extent. In addition, consistent with its epithelial differentiation, the LS-BP-1 model was negative for the expression of H3K27me3. Selinexor was most active than doxorubicin in all models (maximum TVI%: 46% to 84% *vs* 37% to 64%), and the rhabdomyoblastic model showed the highest sensitivity to both agents. Selinexor induced an apoptotic response, as detected by cleaved caspase-3 and PARP-1, in all PDXs and cell lines. Conversely, doxorubicin-induced apoptosis was only observed in the LS-GD-1 model but not in the corresponding cell line. A reduced XPO1 expression, together with an increased nuclear accumulation of p53, was seen in selinexor-treated models. Consistent with the induction of the apoptotic response, a time-dependent depletion of the cytoplasmic anti-apoptotic survivin pool was observed. Interestingly, as a consequence of apoptosis, in LS-GD-1 xenografts and cells, selinexor induced the accumulation of MDM2-p60, a MDM2 fragment generated by caspase-3-mediated cleavage, which loses the ring domain and, consequently, cannot target p53 to proteasome degradation.

Conclusion: These results show a moderate antitumor activity of the XPO1 inhibitor selinexor, which is, however, consistently higher than doxorubicin in different DDLPS preclinical models, independent of the extent of MDM2 amplification and the differentiation subtype. The depletion of survivin protein seems to significantly contribute to the induction of apoptosis through which selinexor exerts its antitumor activity.

Poster #104 3461563

AN UPDATED ANALYSIS OF THE CLINICAL EFFICACY AND SAFETY OF ENTRECTINIB IN NTRK FUSION-POSITIVE (NTRK-FP) SARCOMA

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Objective: Neurotrophic tyrosine receptor kinase (*NTRK1/2/3*) gene fusions lead to constitutively active tropomyosin receptor kinases (TRK) with oncogenic potential. *NTRK* gene fusions occur at low frequencies in a range of common cancers, including <5% of patients with sarcoma. Entrectinib is a CNS-active potent TRK inhibitor. In an integrated analysis of 3 multicenter, single-arm trials (ALKA-372-001 [EudraCT 2012-000148-88], STARTRK-1 [NCT02097810], and STARTRK-2 [NCT02568267]), entrectinib induced clinically meaningful, durable responses in *NTRK*-fp patients across 12 solid tumor types, including sarcoma. We present an updated analysis, with more patients and a longer follow-up, focused on the *NTRK*-fp sarcoma cohort.

Methods: The trials enrolled TRK inhibitor-naïve *NTRK*-fp adults with locally advanced/metastatic solid tumors, with or without baseline CNS metastases. Tumor response was assessed (RECIST v1.1) by blinded independent central review (BICR) after cycle 1 (4 wks) then every 8 wks. Co-primary endpoints (by BICR) were objective response rate (ORR) and duration of response (DoR). Secondary endpoints included progression-free survival (PFS), overall survival (OS) and safety.

Results: At the updated data cut-off (31 Oct 2018), in the overall efficacy-evaluable population (N=74), ORR was 63.5% (n=47/74), including 5 complete responses (CR) and 42 partial responses (PR). Median DoR, PFS and OS were 12.9 (95% CI 9.3–not estimable [NE]), 11.2 (95% CI 8.0–15.7) and 23.9 (95% CI 16.0–NE) months, respectively. In the efficacy-evaluable sarcoma population (n=16) with confirmed *NTRK1* (56.25%) or *NTRK3* (43.75%) gene fusions, median age was 50.5 years (range 21–81 years), 93.8% had ECOG performance status of 0 or 1 and 87.5% had ≤2 prior lines of systemic therapy. Histologies included angiosarcoma (n=1), cervical adenosarcoma (n=1), chondrosarcoma (n=1), endometrial stromal sarcoma (n=1), follicular dendritic cell sarcoma (n=1), malignant peripheral nerve sheath tumor (MPNST; n=1), gastrointestinal stromal tumor (GIST; n=2), spindle cell sarcoma (n=4), undifferentiated pleomorphic sarcoma (n=1) and sarcoma, not otherwise specified (NOS; n=3 [2 with carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements]). Two patients (12.5%) had baseline CNS metastases, as assessed by investigator and BICR (1 spindle cell sarcoma, 1 undifferentiated pleomorphic sarcoma). After a median follow-up of 17.74 months, ORR was 56.25% (95% CI 29.9–80.3; see **table**). In the 9 responders (all PR), median time to response was 0.95 (95% CI 0.9–2.8) months and median DoR was 9.3 (95% CI 4.6–15.0) months. PFS and OS were 10.1 (95% CI 6.5–11.2) and 16.8 (95% CI 10.6–20.9) months, respectively. Of the 2 patients with baseline

CNS metastases, 1 patient (undifferentiated pleomorphic sarcoma, received prior radiotherapy [RT]) had a systemic PR and intracranial PR, while the other (spindle cell sarcoma, no prior RT) had a systemic PR and intracranial non-CR/non-PD (non-measurable brain metastases). Safety populations comprised patients who received ≥1 dose of entrectinib. The overall safety-evaluable population comprised 504 patients (475 adults, 29 children), of whom 90.5% reported treatment-related adverse events (TRAEs) grade ≤4. The safety-evaluable sarcoma population comprised 18 patients, of whom 16 (88.9%) reported TRAEs grade ≤4. The most frequently reported TRAEs were dysgeusia (44.4%), dizziness (38.9%), fatigue (33.3%), peripheral edema (27.8%) and weight gain (27.8%). Dose reductions, interruptions, and discontinuations due to TRAEs occurred in 22.2%, 16.7% and 5.6% of patients, respectively.

Conclusion: Entrectinib continued to achieve clinically meaningful, durable responses in patients with *NTRK*-fp sarcoma, demonstrating both systemic and intracranial efficacy in patients with baseline CNS metastases. It was well tolerated, with a manageable safety profile.

Systemic efficacy in NTRK-fp patients with sarcoma, by tumour histology

NTRK-fp sarcoma (N=16)		
Response		Tumour histology (n)
BICR ORR, n/N (%) (95% CI)	9/16 (56.25) (95% CI 29.9–80.3)	Cervical adenosarcoma (1) Endometrial stromal sarcoma (1) GIST (2) Spindle cell sarcoma (2) Undifferentiated pleomorphic sarcoma (1) Sarcoma, NOS (1) Sarcoma, NOS with carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements (1)
PR, n/N (%)	9/16 (56.25)	Cervical adenosarcoma (1) Endometrial stromal sarcoma (1) GIST (2) Spindle cell sarcoma (2) Undifferentiated pleomorphic sarcoma (1) Sarcoma, NOS (1) Sarcoma, NOS with carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements (1)
SD, n/N (%)	4/16 (25.0)	Angiosarcoma (1) Follicular dendritic cell sarcoma (1) MPNST (1) Sarcoma, NOS with carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements (1)
PD, n/N (%)	1/16 (6.25)	Chondrosarcoma (1)
Missing/not evaluable, n/N (%)	2/16 (12.5)	Spindle cell sarcoma (2)
GIST, gastrointestinal stromal tumor; MPNST, malignant peripheral nerve sheath tumor; NOS, not otherwise specified; SD, stable disease; PD, progressive disease		

Poster #105 3461635

LAROTRECTINIB EFFICACY AND SAFETY IN ADULT PATIENTS WITH TRK FUSION SARCOMAS

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Objective: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a diverse range of tumor types. Larotrectinib, a highly selective, CNS-active tropomyosin receptor kinase (TRK) inhibitor approved for adults and children by the FDA and EMA, demonstrated an objective response rate (ORR) of 79% and a median duration of response (DoR) of 35.2 months across various cancers (Hong DS et al. *Lancet Oncol.* 2020). We report the efficacy and safety of larotrectinib in adult patients with TRK fusion sarcomas from an expanded dataset.

Methods: Adult patients ≥18 years old with sarcomas harboring *NTRK* gene fusions and treated with larotrectinib were identified from three clinical trials (NCT02122913, NCT02576431, NCT02637687). Patients received larotrectinib 100 mg PO twice daily (one patient received 150 mg PO twice daily). Response was investigator assessed per RECIST v1.1.

Results: By July 15, 2019, 25 adult patients with TRK fusion sarcomas had been treated: 2 bone sarcomas, 4 gastrointestinal stromal tumors (GISTs), and 19 soft tissue sarcomas (malignant peripheral nerve sheath tumor [n=4], epithelioid spindle sarcoma [n=3], not otherwise specified [n=2], stromal tumor [n=2], and adult fibrosarcoma, liposarcoma, myopericytoma, inflammatory myofibroblastic tumor, inflammatory myofibroblastic tumor of the kidney, pleomorphic sarcoma, spindle cell sarcoma, and synovial sarcoma [each n=1]). Median age was 45 (range 19–61) years. In total, 12 (48%) patients had received ≥2 prior systemic therapies. ORR was 72% (95% CI 51–88): 4 (16%) patients had complete responses and 14 (56%) patients had partial responses (**Table**). Median DoR was not estimable (NE; 95% CI 7.2–NE) with a 12-month DoR rate of 64% (95% CI 37–82). Median progression-free survival was 28.3 months (95% CI 6.8–NE) and median overall survival was 44.4 months (95% CI 44.4–NE). Treatment duration ranged from 0.1 to 51.6+ months. Adverse events (AEs) were mostly Grade 1–2. Grade ≥3 treatment-emergent AEs occurred in 11 (44%) patients, with none attributed to larotrectinib. No patients discontinued treatment due to a larotrectinib-related AE.

Conclusion: Larotrectinib resulted in robust and durable responses with a favorable safety profile in adult patients with TRK fusion sarcomas, including soft tissue sarcomas of various histologies, GISTs, and bone sarcomas. These data highlight the clinical importance of identifying *NTRK* gene fusions in patients with sarcomas, to enable these patients potentially to benefit from TRK-targeted therapy.

TABLE:

	Soft tissue sarcomas (n=19†)	GISTs (n=4)	Bone sarcomas (n=2)	All adult sarcomas (n=25†)
ORR, n (%)	13 (68)	4 (100)	1 (50)	18 (72)
CR	3 (16)	1 (25)	0	4 (16)
PR	10 (53)	3 (75)	1 (50)	14 (56)
SD	3 (16)	0	1 (50)	4 (16)
PD	2 (11)	0	0	2 (8)

†One patient not determined.
CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Poster #106 3461675

IMPACT OF NEXT GENERATION SEQUENCING (NGS) ON THE TREATMENT OF PATIENTS WITH SARCOMA

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Objective: To better delineate the role, and impact of NGS on the treatment of patients with sarcoma.

Methods: In this retrospective review, we analyzed the NGS profiles of patients seen through the Northwestern Healthcare System obtained through multiple assays, including Foundation Medicine, Tempus, and Guardant 360. NGS were screened for potentially germline, and somatic variants of known and undetermined significance. These variants were cross-referenced with ongoing tumor agnostic, or sarcoma-specific trials. Of those patients who qualified for targeted therapy, we evaluated for clinical outcomes, and alteration in management.

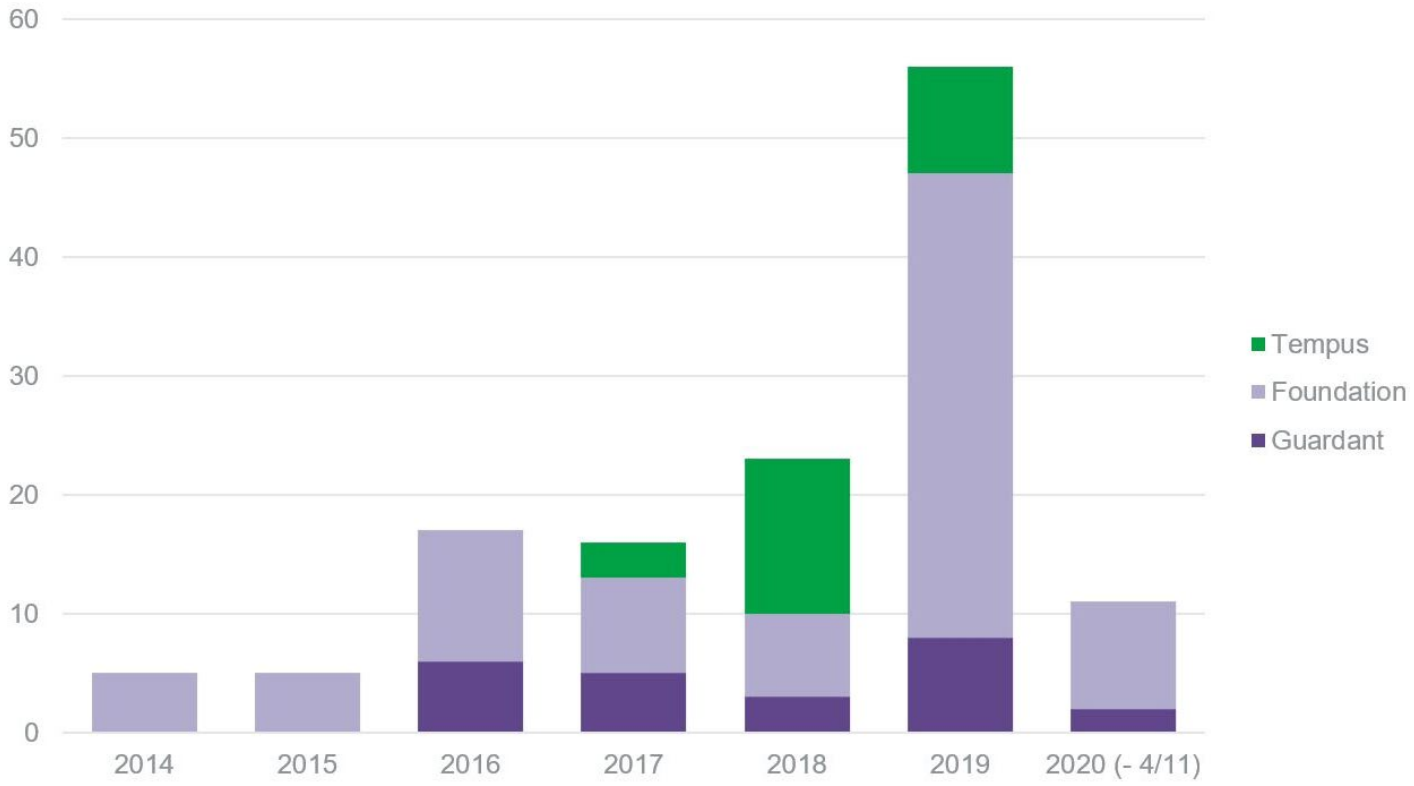
Results: Between 2014, and 2020, 117 patients with a diagnosis of sarcoma had NGS performed through Northwestern. Between these 117 patients, 134 assays were performed. Median age of those sampled was 55 (20-94), with a population that was 52% female to 48% male. The most frequently sampled tumor was Leiomyosarcoma. In total, 2504 mutations were found in 482 unique genes, with a median of 12, 6, and 3 mutations per patient for Foundation Medicine, Tempus, and Guardant assays, respectively. The most commonly detected mutations were in p53. Amongst our patient population, there were 40 with actionable mutations, most of which through tissue agnostic trials. In total, 9 of 117 patients had alterations in their management as a result of performance of NGS.

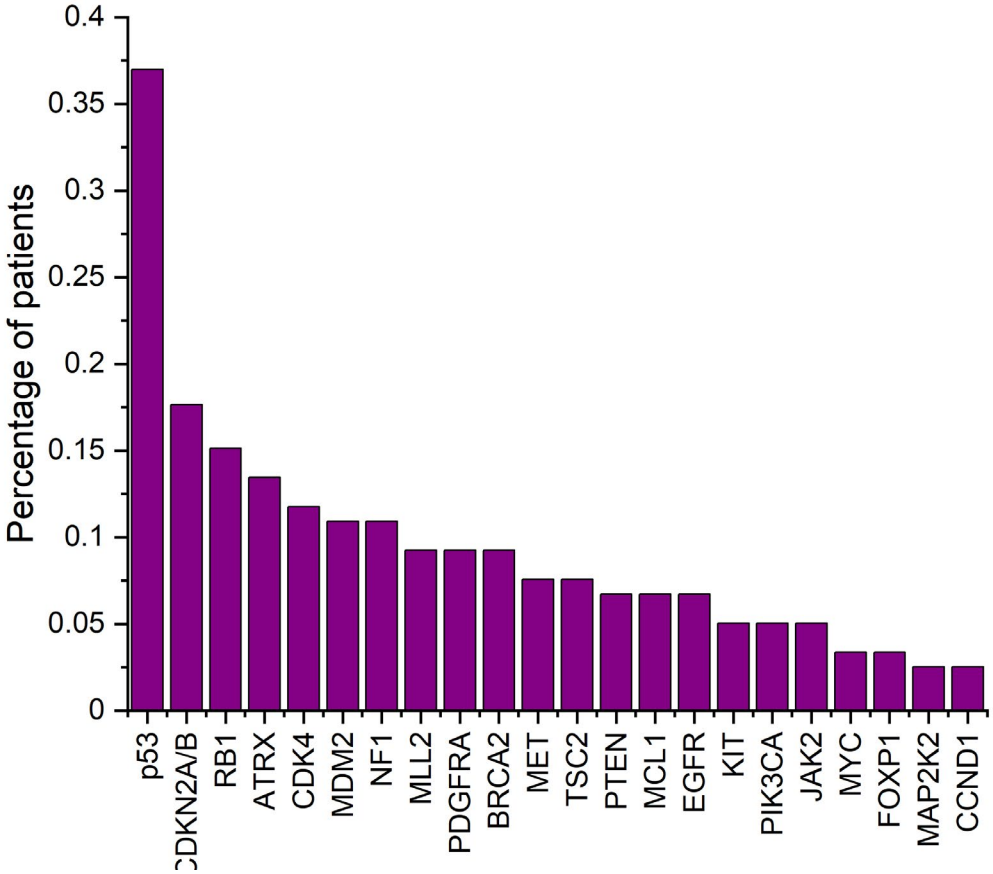
Conclusion: The data acquired in this study reveal that NGS identifies actional mutations in 34% of patients, and makes a significant impact in the management of 8% of patients with Sarcoma.

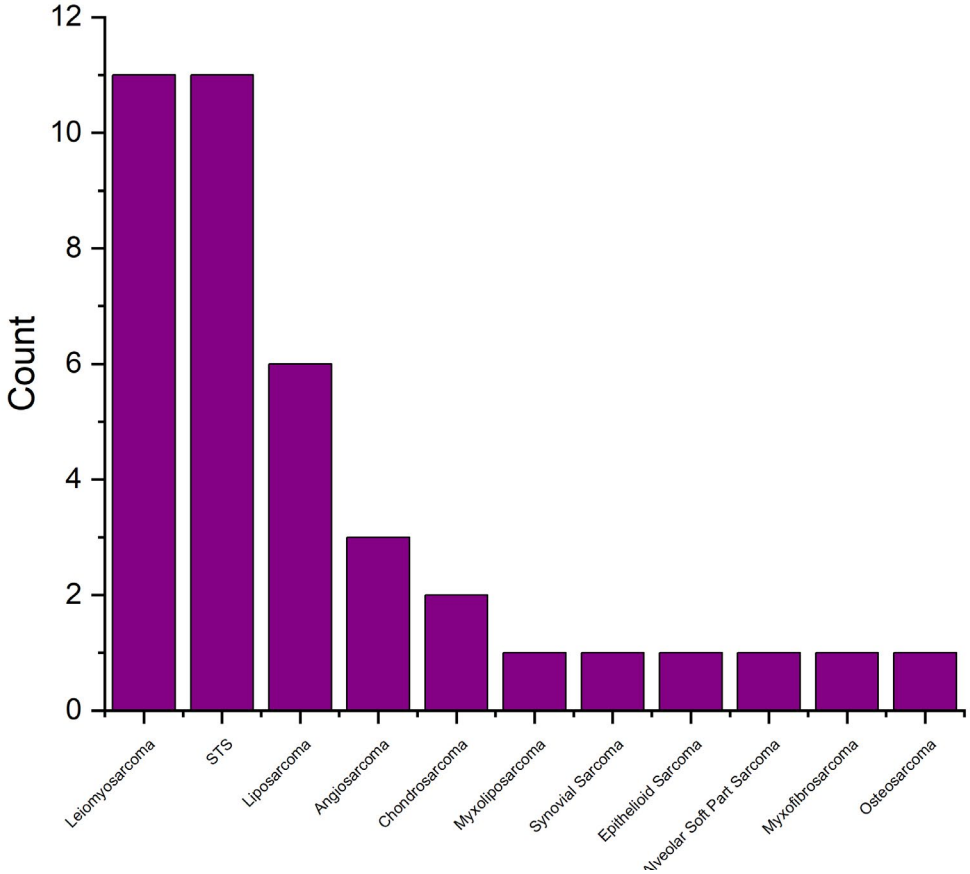
Histology	Target	Treatment
Ewings	PTEN loss	Copanlisib
Leiomyosarcoma	ALK Fusion	Alectinib
Leiomyosarcoma	MSI-H	Nivolumab
Chondrosarcoma	IDH1	Ivosidenib
Synovial Sarcoma	BRAF V600E	Encorafenib
STS NOS	CDK4 Amplification	Palbociclib
STS NOS	CCND1 Amplification	Palbociclib
STS NOS	NTRK Fusion	Larotrectinib
Myxofibrosarcoma	High TMB	Atezolizumab

Table 1

Age	
Median	55 (20, 94)
Sex	
Female	60 (52%)
Male	57 (48%)
Assays Per Patient	
Median	1 (1, 4)
Patients with more than 1 assay	13 (11%)
Histologic Subtype	
Leiomyosarcoma	46 (31%)
STS NOS	21 (18%)
Angiosarcoma	13 (11%)
Liposarcoma	11 (9%)
Other	36 (31%)
No variants detected	
Guardant	6 (25%)
Tempus	1 (2%)




Percentage of patients
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
p53
CDKN2A/B
RB1
ATRX
CDK4
MDM2
NF1
MLL2
PDGFRA
BRCA2
MET
TSC2
PTEN
MCL1
EGFR
KIT
PIK3CA
JAK2
MYC
FOXP1
MAP2K2
CCND1


Count
12
10
8
6
4
2
0
Leiomyosarcoma
STS
Liposarcoma
Angiosarcoma
Chondrosarcoma
Myxoliposarcoma
Synovial Sarcoma
Epithelioid Sarcoma
Alveolar Soft Part Sarcoma
Myxofibrosarcoma
Osteosarcoma

Poster #107 3461682

HISTOLOGY AND TUMOUR BIOLOGY ARE MORE IMPORTANT IN PREDICTING OVERALL SURVIVAL THAN MARGINS OF RESECTION

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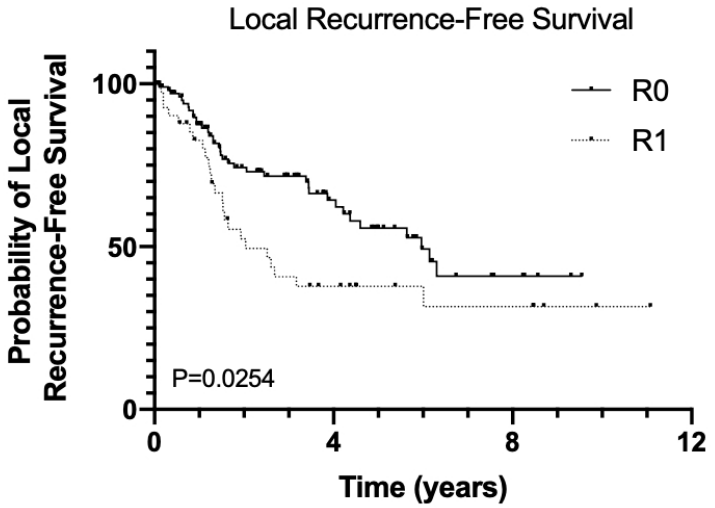
Objective: Controversy exists regarding the role of microscopic positive (R1) resection margins on Overall Survival (OS) of Retroperitoneal Liposarcoma (RPLPS). Due to limitations in pathologic margin sampling, some experts argue that a true microscopic negative (R0) resection for RPLPS is rare. Additionally, the assessment of whether R1 status is truly an independent predictor of OS is confounded by factors such as patient comorbidity and tumor biology. The objective of this study was to determine the clinicopathological factors influencing microscopic resection margins and prognostic outcomes in RPLPS.

Methods: We collected data on all patients undergoing surgery for primary RPLPS between 2005-2020 at The Ottawa University Hospital, Canada and University Hospital Birmingham NHS Foundation Trust, United Kingdom. Well-differentiated (WDLPS) and Dedifferentiated Liposarcoma (DDLPS) were included. All other histological subtypes and those with macroscopically incomplete resection margins (R2) were excluded. Uni- and multivariable logistic regression analyses were used to identify whether clinicopathological factors were associated with microscopically present margins (R1), and their association with 5-year local recurrence-free (RFS) and OS outcomes. Kaplan-Meier survival curves were plotted and analyzed using the log-rank test.

Results: 151 patients were retrospectively reviewed, of which 62 patients (41.1%) had WDLPS histological subtype. Median follow-up time was 38.5 months. 110 patients (72.8%) had negative R0 margins and 41 patients (27.2%) had microscopically positive (R1) margins. Of the WDLPS patients, only 14.5% had a R1 margin compared to 36.0% in the DDLPS cohort. DDLPS histological subtype was found to be significantly associated with R1 status on multivariable logistic regression (P=0.0081) with an odds ratio of 20.13 [95% CI, 3.093 – 404.1]. Median local RFS for R0 vs. R1 patients was 17.7 vs. 15.7 months respectively (log rank P=0.0254). When accounting for other clinicopathological factors, R1 margins (P=0.0210); tumour size over 20cm (P=0.0240); DDLPS histological subtype (P=0.0311) and tumour multifocality (P=0.0322) were found to be independently associated with 5-year local RFS. For OS, there was no significant difference between R0 and R1 cohorts (log rank P=0.1246). On multivariable analysis, R1 status (P=0.6118) was not associated with a worse 5-year OS; however, DDLPS histological subtype (P=0.0039) and high Charlson Comorbidity Index (P=0.0010) were found to be significantly associated with a worse 5-year OS.

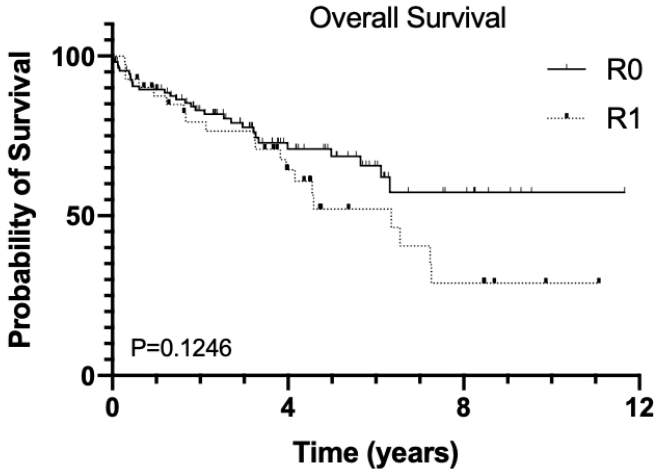
Conclusion: Pathological assessment of margins is challenging in RPLPS and subject to interpretation. These results demonstrate that resection margins may be more dependent on tumour biology factors, namely histological subtype rather than surgical technique. These results also suggest that R1 resection margins may influence local tumour control outcomes and not overall survival. A complete macroscopic resection (R0/R1) done in an expert sarcoma center remains the mainstay of treatment and considered a high-quality surgery for primary RPLPS for the best possible outcome.

Figure 1. Kaplan-Meier curve of local recurrence-free survival between R0 vs. R1 cohorts. Univariable and multivariable logistical regression models between clinicopathological factors and 5-year local recurrence-free survival. * denotes significance.



Clinicopathological Factor	Multivariable p-value	Odds Ratio (95% CI)
Resection margin (R1)	0.0210*	2.801 (1.181 – 6.892)
Tumour size (>20cm)	0.0240*	2.781 (1.169 – 6.985)
High tumour grade (FNCLCC 2/3)	0.6637	1.413 (0.2567 - 6.355)
Dedifferentiated liposarcoma subtype	0.0311*	5.677 (1.291 – 32.81)
Neoadjuvant Chemotherapy	0.6909	1.833 (0.1142 – 64.11)
Neoadjuvant Radiation Therapy	0.1052	0.2286 (0.028 – 1.171)
Multivisceral Resection (>1 organ resected)	0.1631	0.3561 (0.083 – 1.618)
Tumour multifocality	0.0322*	9.036 (1.312 – 85.41)

Figure 2. Kaplan-Meier curve of overall survival between R0 vs. R1 cohorts. Univariable and multivariable logistical regression models between clinicopathological factors and 5-year overall survival. * denotes significance.



Clinicopathological Factor	Multivariable p-value	Odds Ratio (95% CI)
Resection margin (R1)	0.6118	1.280 (0.4915 – 3.344)
Tumour size (>20cm)	0.2798	1.773 (0.6376 – 5.192)
High tumour grade (FNCLCC 2/3)	0.8141	0.7735 (0.078 – 6.643)
Dedifferentiated liposarcoma subtype	0.0039*	65.22 (5.625 – 2080)
Neoadjuvant Radiation Therapy	0.3754	0.4394 (0.054 – 2.366)
Multivisceral Resection (>1 organ resected)	0.4204	0.3864 (0.035 – 4.509)
Body Mass Index (>30)	0.0813	0.2939 (0.065 – 1.080)
High Charlson Comorbidity Index	0.0010*	5.863 (2.144 – 17.62)

Poster #108 3461698

HISTOLOGIC MARKERS PREDICTIVE OF WOUND HEALING COMPLICATIONS IN SOFT TISSUE SARCOMA TREATED WITH PREOPERATIVE RADIATION

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Objective: Soft tissue sarcoma (STS) is a rare cancer frequently requiring resection. Postoperative wound healing complication (WHC) incidence is high due to surgical morbidity. Resection often follows preoperative radiation (Pre-XRT). This sterilizes resection margins to reduce recurrence, but WHC incidence increases to one third of patients. Radiation is implicated in WHC, but its true mechanism remains unknown. We investigated if clinical or histological factors in skin specimens of STS patients predict WHC as it may add to current knowledge and generate new interventions. Factors were compared in patients with and without Pre-XRT, plus WHC were assessed in Pre-XRT patients. We also evaluated dermal fibroblast nuclear expression of transcriptional coactivator with PDZ-binding motif (TAZ), a transcriptional regulator in the Hippo pathway.

Methods: This retrospective study of 55 adult patients following STS resection with primary closure evaluated clinical features including age, sex, tumor factors, and treatment including Pre-XRT or neoadjuvant chemotherapy. A pathologist with dermatopathology expertise evaluated histopathology and was blind to clinical outcomes. Hematoxylin and eosin sections of STS resected skin were assessed for inflammation (location, cells/high-power field [HPF], cell type), dermal thickness, and vessel density (vessel cross sections/HPF). Elastichrome stains assessed elastin organization. TAZ immunohistochemistry was measured in dermal fibroblasts. The sum of primary and secondary H-scores (intensity * % of cells staining at that intensity) represented total H-score. Case-control analysis compared patients for development of WHC within 4 months of surgery. Chi-square, Fisher's Exact, and Wilcoxon Sum Rank were used for variable comparison.

Results: First, comparing skin treated with and without Pre-XRT (Table 1), mean TAZ H-scores were higher following Pre-XRT (276.5 vs 253.9; p=0.017). Similarly, plasma cells were more often present in radiated skin (p=0.0006). Compared to non-radiated skin, radiated skin demonstrated a greater absence of hair follicles (p=0.0198) and sebaceous glands (p=0.0159) plus a decrease in vascularity (p=0.0323). The presence or absence of Pre-XRT did not show significant differences in patient clinical characteristics. Next, comparing the development or avoidance of WHC in the Pre-XRT cohort (Table 2), those without WHC had greater mean TAZ H-scores than patients with WHC (282.5 vs 260; p=0.0402). This cohort also trended toward more organized elastin, more frequent presence of neutrophils and hair follicles, and <100 inflammatory cells/HPF in those with WHC.

Conclusion: Our most novel findings center on TAZ. Normally, Hippo inactivation allows YAP/TAZ complex localization to the nucleus where it functions as a transcriptional co-activator for genes involved in angiogenesis and tissue remodeling. This is an important step in a complex pathway that is not fully understood. Prior studies in animal models and human cell cultures demonstrate increased TAZ expression in early cutaneous wound healing and loss of TAZ in impaired wound closure. Thus, higher TAZ in our radiated versus non-radiated patients may reflect a response to injury while TAZ decreases might contribute to WHC following Pre-XRT. To our knowledge, plasma cells have not been described in cutaneous infiltrates following radiation. The significance of this finding is unclear. Neutrophils aid in early wound healing, but their persistence may contribute to chronic non-healing wounds. The trend toward greater frequency of neutrophils in skin with WHC raises the possibility they contribute to WHC. Decreased hair follicles, sebaceous glands, and vessel density concur with prior descriptions of radiated skin. Although TAZ expression differences in this cohort are not discriminative enough to be a stand-alone predictor of WHC, TAZ may help predict WHC when used with other histologic factors, and ultimately may suggest a contributory pathway and therapeutic target.

Table 1. Comparison of histologic characteristics between patients receiving and not receiving preoperative radiation (Pre-XRT) n = 55. Significance $p < 0.05$.

Characteristic	Pre-XRT n = 31	No Pre-XRT n = 24	p-value
Elastin Organization			
0-1	23	15	0.2573
2-3	7	9	
Neutrophils			
Yes	7	1	0.1191
No	24	23	
Plasma Cells			
Yes	12	0	p = 0.0006, OR = 31.4 (1.75 - 565.4)
No	19	24	
Inflammatory Cells			
>100/HPF	13	8	0.5149
≤100/HPF	18	16	
Hair Follicles			
Yes	15	19	p = 0.0198, OR = 4.05 (1.21 - 13.61)
No	16	5	
Eccrine Glands			
Yes	31	23	0.4364
No	0	1	
Sebaceous Glands			
Yes	1	7	p = 0.0159, OR = 12.35 (1.4 - 109.1)
No	30	17	
Dermal Thickness (cm)			
≥4	6	7	0.3956
<4	25	17	
Vessels/HPF			
>30	2	7	p = 0.0323, OR = 5.97 (1.11 - 32.09)
≤30	29	17	
Total H-score			
Mean ± SD	276.5 ± 38.8	253.9 ± 48.5	0.017

Table 2. Comparison of histologic features in patients treated with preoperative radiation with and without wound healing complications (WHC) n = 31. Significance $p < 0.05$.

Characteristic	WHC n = 9	No WHC n = 22	p-value
Elastin Organization			
0-1	8	15	0.1434
2-3	0	7	
Neutrophils			
Yes	4	3	0.1504
No	5	19	
Plasma Cells			
Yes	4	8	0.7039
No	5	14	
Inflammatory Cells			
>100/HPF	2	11	0.2374
≤100/HPF	7	11	
Hair Follicles			
Yes	6	9	0.2524
No	3	13	
Eccrine Glands			
Yes	9	22	NA
No	0	0	
Sebaceous Glands			
Yes	1	0	0.2903
No	8	22	
Dermal Thickness (cm)			
≥4	2	4	1
<4	7	18	
Vessels/HPF			
>30	1	1	0.5032
≤30	8	21	
Total H-score			
Mean ± SD	260 ± 57.32	282.5 ± 29.02	0.0402

Poster #109 3461710

INTEGRATED SAFETY ANALYSIS OF TAZEMETOSTAT 800 MG TWICE DAILY IN ADULT PATIENTS WITH HEMATOLOGIC AND SOLID TUMORS

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Objective: Tazemetostat, a first-in-class EZH2 inhibitor, is the only FDA-approved treatment for epithelioid sarcoma and is under review for approval for follicular lymphoma. We analyzed adverse events (AEs) from clinical trials of single-agent tazemetostat in a larger population of patients with hematologic malignancies and genetically defined tumors.

Methods: Treatment-emergent AEs (TEAEs) were compiled from 6 studies. The analysis cohort included patients ≥18 years who had received ≥1 dose of tazemetostat 800 mg twice daily. TEAEs are reported descriptively.

Results: Safety was assessed in 690 patients with non-Hodgkin lymphoma (n=358, including follicular lymphoma [n=109]), epithelioid sarcoma (n=104), and other solid tumors (n=228). Median drug exposure was 3.5 (range, 0.02–52.2) months; 605 (88%) patients completed ≥90% of the planned dose. TEAEs led to dose reduction in 30 (4%) patients, drug interruption in 220 (32%), and drug discontinuation in 40 (6%).

The most common TEAEs were nausea, fatigue, and vomiting observed early in treatment (≤4 months). Grade 3–4 TEAEs were reported in 359 (52%) patients; 126 (18%) were assessed as drug-related. Five patients (4 with primary lymphomas) had AEs of special interest per protocol (acute myeloid leukemia, n=2; myelodysplastic syndrome, n=2; myelodysplastic syndrome to acute myeloid leukemia transformation, n=1); these were confounded by prior treatments and baseline hematologic abnormalities. One pediatric chordoma patient (900 mg/m^2 twice daily for 15 months) excluded from this analysis of adults had a secondary T-cell lymphoblastic lymphoma. Two patients died of related TEAEs (intestinal obstruction and reason unknown) during or ≤30 days after treatment. The overall safety profile was similar in patients with hematologic vs solid tumors, with differences attributed to underlying disease and/or comorbidities.

Conclusion: The most common TEAEs were mild/moderate and resolved with standard medical care and/or dose modification. Dose reductions/discontinuations due to TEAEs were uncommon. Tazemetostat was generally well tolerated with an overall safety profile consistent across indications.

Table.

	All TEAEs* N=690		Treatment-related TEAEs N=690	
	All grades	Grade 3–4	All grades	Grade 3–4
Patients with TEAEs, n (%)	661 (96)	359 (52)	455 (66)	126 (18)
Adverse event, n (%)				
Nausea	186 (27)	8 (1)	127 (18)	5 (0.7)
Fatigue	164 (24)	16 (2)	107 (16)	7 (1)
Vomiting	136 (20)	6 (1)	54 (8)	3 (0.4)
Diarrhea	120 (17)	7 (1)	54 (8)	5 (0.7)
Cough	118 (17)	1 (0.1)	15 (2)	0
Anemia	114 (17)	54 (8)	62 (9)	28 (4)
Decreased appetite	105 (15)	7 (1)	52 (8)	1 (0.1)
Thrombocytopenia	77 (11)	38 (6)	54 (8)	23 (3)
Neutropenia	51 (7)	40 (6)	41 (6)	29 (4)

*TEAEs occurring in ≥15% of patients and grade 3–4 TEAEs occurring in ≥5% of patients are shown. TEAEs were defined as adverse events that started or worsened on or after the day of the first tazemetostat dose up to 30 days after the last dose.

Poster #110 3461748

RECRUITMENT PATTERNS IN A LARGE INTERNATIONAL RANDOMIZED CONTROLLED TRIAL OF PERIOPERATIVE CARE IN CANCER PATIENTS

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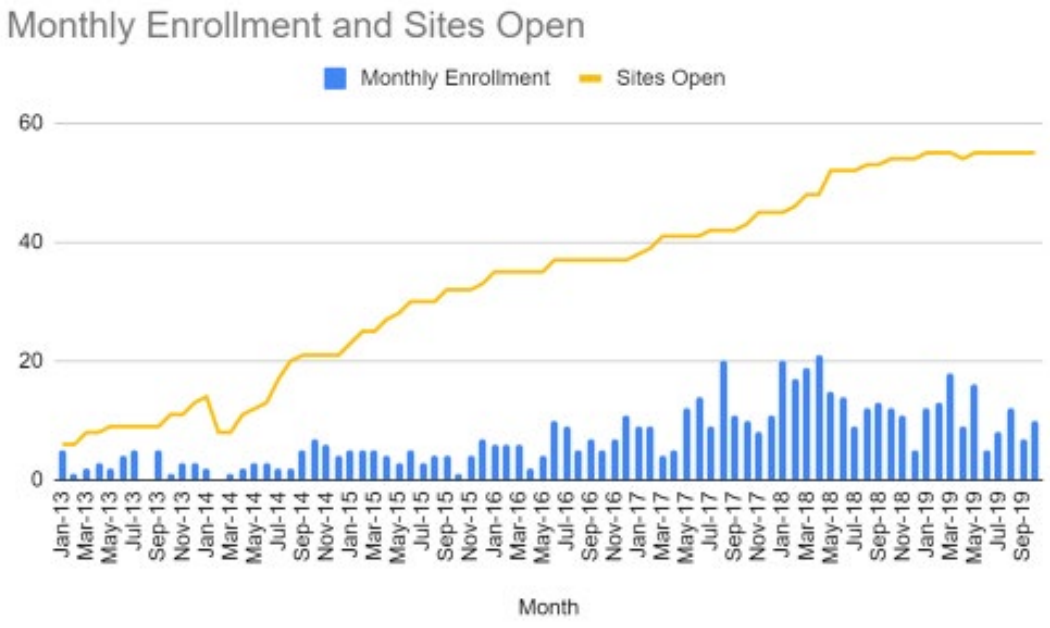
Objective: The Prophylactic Antibiotic Regimens in Tumor Surgery (PARITY) randomized controlled trial (RCT) was the first study to prospectively enroll and randomize orthopaedic oncology patients in multiple centers internationally. The objective of this study was to describe recruitment patterns, examine the differences in enrollment across different PARITY sites, and to identify variables associated with differing levels of recruitment.

Methods: Data from this study was obtained from the PARITY trial Methods Center and records of correspondence between the Methods Center and recruiting sites. We performed descriptive statistics to report the recruitment patterns over time. We compared recruitment, time to set up, and time to enroll the first patient between North American and international sites, private and public health care models, and the presence or absence of research personnel. Two-tailed non-paired t-tests were performed to test average monthly recruitment rates between groups.

Results: A total of 602 patients from 36 North American and 12 international sites were recruited from 2013 to 2019. Average monthly enrollment increased each year of the study (**Figure 1**). North American sites were able to start up significantly faster than international sites (19.5 vs. 27.0 months p=0.04). However, international sites had a significantly higher recruitment rate once active (0.2 participants/month vs. 0.59 participants/month, p=0.023). Sites with research personnel were able to reach 'enrolment ready' status significantly faster than sites without research personnel (19.3 vs. 30.3 months, p=0.032), but there was no difference in recruitment once active (0.28 participants/month vs. 0.2 participants/month). Publicly funded sites were to recruit significantly more patients compared to private institutions (0.4/month vs. 0.17/month, p=0.03).

Conclusion: As a collaborative group, the PARITY investigators increased the pace of recruitment throughout the trial, likely by increasing the number of active sites. The longer time to start-up at international sites may be due to the complex governing regulations of pharmaceutical trials. Nevertheless, international sites should be considered essential as they recruited significantly more patients per month once active. The absence of research support personnel may lead to delays in time to start up. The results of the current study will provide guidance for choosing which sites to recruit for participation in future collaborative clinical trials in orthopaedic oncology and other surgical specialties.



Poster #111 3461782

FACTORS INFLUENCING UNPLANNED READMISSION AFTER SURGERY IN SOFT TISSUE SARCOMAS

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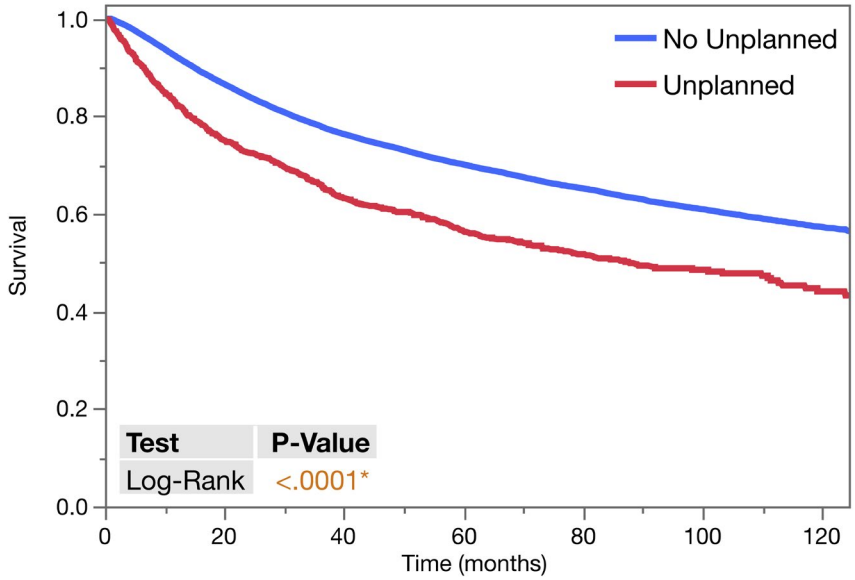
Objective: Soft-tissue sarcomas (STS) often require extensive surgical procedures and hospitalization for treatment of these malignant tumors. While many studies examine the effects of surgical resection and negative margins on patient survival, less is known regarding the perioperative complications and factors that lead to increased morbidity and unplanned re-admission. The purpose of this study was to identify the patient, tumor, and treatment variables that may correlate with readmission after surgery for patients with STS.

Methods: We retrospectively reviewed 46,869 patients who underwent surgical treatment of primary malignant soft-tissue sarcomas in the National Cancer Database (NCDB) from 2004 through 2015. Univariate analysis by Pearson Chi-Square method assessed differences between cohorts. Survival differences between patients with or without unplanned readmissions were compared using the Kaplan-Meier method. Multivariate analysis with multiple imputation and nominal logistic regression was used to assess patient, tumor and treatment variables for their influence on readmission rates.

Results: A total of 1,440 patients had an unplanned readmission within 30 days of discharge after surgery, compared with 1,110 who only had planned readmissions, and 42,906 who were not readmitted post-operatively. Patients who had unplanned readmissions had a worse 5-year survival rate and worse overall median survival than those without unplanned readmission (56% vs. 70% at 5 years, and overall median survival 7.3 years vs. 12.6 years, log-rank <0.001). In a multivariate analysis, factors with increased odds of unplanned readmission included higher comorbidity score (OR 2.03 [1.62-2.54], p<0.001 for CCS ≥2 vs. 0), non-private insurance (uninsured OR 1.38 [1.08-1.77], p=0.010; government OR 1.21 [1.06-1.38], p=0.004), academic facility type (OR 1.14 [1.01-1.3], p=0.038), tumor location in abdomen or pelvis (vs. limb, OR 1.35 [1.18-1.54], p<0.001), and presence of metastases (OR 1.74 [1.42-2.12], p<0.001) (Figure 2). Age, sex, race, and neoadjuvant radiation or chemotherapy were not statistically significant predictors of readmission.

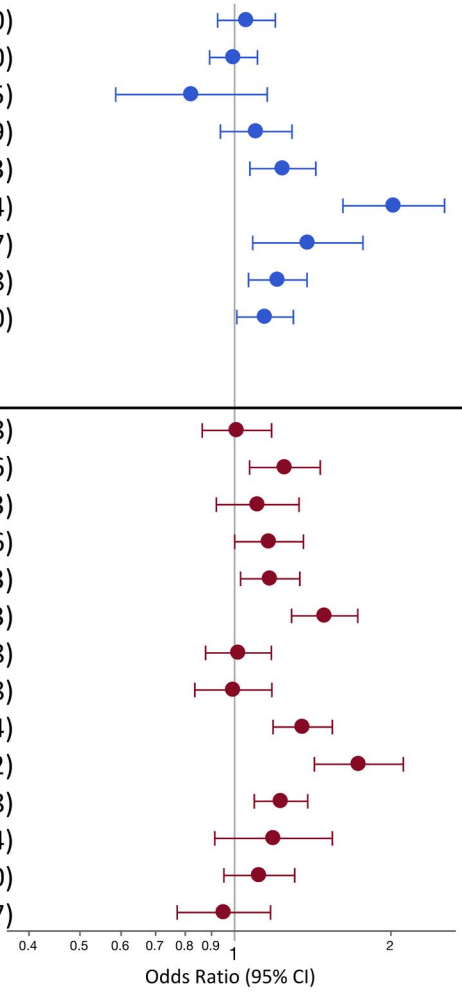
Conclusion: Unplanned readmission after surgical treatment of soft-tissue sarcomas is associated with a number of patient, tumor, and treatment characteristics. As patients who undergo unplanned readmission have poorer survival than those without unplanned readmission, those with significant comorbidities or abdominopelvic tumors should receive careful perioperative optimization and discharge planning to minimize the likelihood of unplanned readmission.

5-year survival of patients who underwent surgical treatment of soft-tissue sarcoma (STS), by readmission status.
Patients who had unplanned readmissions had worse survival compared to those who did not have unplanned readmission (56% vs. 70%, Log-rank p<0.001). Overall median survival was 88 months for patients with unplanned admissions vs. 151 months for those without.



Predictors of unplanned readmission in multivariate analysis.
Patient, tumor and treatment variables were assessed for their influence on unplanned readmissions by logistic regression. Odds ratios and 95% confidence intervals are shown and demonstrated in the forest plot. P-values provided with statistical significance noted as *p<0.05, **p<0.01, ***p<0.001.

Patient Demographic Variables		OR (95% CI)	P-Value
Age below median (for histology)		1.05 (0.92-1.20)	0.442
Male sex		0.99 (0.89-1.10)	0.897
Race (vs. White)	Asian	0.82 (0.59-1.15)	0.259
	Black	1.10 (0.94-1.29)	0.249
Comorbidity Score (vs. 0)	1	1.24 (1.07-1.43)	0.005 **
	≥2	2.03 (1.62-2.54)	<0.001 ***
Insurance (vs. Private)	None	1.38 (1.08-1.77)	0.010 **
	Govt.	1.21 (1.06-1.38)	0.004 **
Academic facility type		1.14 (1.01-1.30)	0.038 *
Tumor and Treatment Variables			
Tumor size (vs. <5 cm)	5-10 cm	1.01 (0.86-1.18)	0.920
	>10 cm	1.25 (1.07-1.46)	0.006 **
Grade (vs. Low)	Intermed.	1.11 (0.92-1.33)	0.285
	High	1.16 (1.00-1.36)	0.053
Extension (vs. Confined)	Localized	1.17 (1.02-1.33)	0.020 *
	Adjacent Spread	1.49 (1.29-1.73)	<0.001 ***
Location Deep (vs. Superficial)		1.01 (0.88-1.18)	0.842
Site (vs. Limb)	Head, Neck, Thorax	0.99 (0.84-1.18)	0.927
	Abdomen, Pelvis	1.35 (1.18-1.54)	<0.001 ***
Metastases		1.74 (1.42-2.12)	<0.001 ***
Surgery (vs. Local)	Wide Resection	1.23 (1.09-1.38)	0.001 **
	Amputation	1.19 (0.91-1.54)	0.200
Neoadjuvant Radiation		1.11 (0.95-1.30)	0.181
Neoadjuvant Chemotherapy		0.95 (0.77-1.17)	0.636



Poster #112 3461852

18F-FDG PET/CT CAN HELP SOLVE THE GRADING DILEMMAS IN CARTILAGE BONE NEOPLASMS? SURGEON'S INTERPRETATION FOR TREATMENT PLANNING

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Objective: Cartilage lesions vary in the spectrum from benign enchondromas to highly malignant dedifferentiated chondrosarcomas. From the treatment perspective, enchondromas are observed, Grade 1 chondrosarcomas are curetted like aggressive benign tumors, and rest are resected like other sarcomas. In the absence of definite pre-treatment grading, a surgeon is therefore often in a dilemma when deciding the best treatment option. PET-CT has been used to try and grade these tumors based on the metabolic activity but there have been very few published reports with a large number of cases.

The authors asked these study questions:
(1) Does maximum standardized uptake value (SUVMax) from an 18F-FDG PET/CT by itself correlate with the grade of chondrosarcoma?
(2) Does the addition of 18F-FDG PET/CT guide the clinician to offer histology equivalent value for treatment by differentiating between benign and low grade (grade 1) chondrosarcomas; and low grade (grade 1) versus intermediate and higher grade chondrosarcomas (IHGCS: Grades 2 and 3)?
(3) In which subset of chondroid tumors would an 18F-FDG PET/CT be useful in the diagnostic workup?

Methods: This is a retrospective study of patients with suspected chondrosarcoma. The SUVmax values were correlated with the final histology grade for the operated patients. Radiological parameters (and radiology aggressiveness scores RAS) were re-evaluated and tabulated. 106 patients 68 males and 38 females with a mean age of 46.55 years (13 to 74 years) with chondroid tumors underwent 18F-FDG PET/CT assessment. 73 patients had tissue diagnosis available as a pre-treatment investigation in addition to local imaging (radiographs and/or CT scans and MRI scans). 20 patients with no disease progression at a minimum of 6 months follow-up were classified as benign enchondromas for final analysis.

Results: Results of Spearman correlation indicated that there was a significant positive association between SUVMax and final histology grading of chondroid tumors, (correlation coefficient = .743, $p < 0.01$).
SUVMax is a weak investigation to differentiate between benign and low grade (grade 1) chondrosarcomas for all chondroid neoplasms. The presence of 1 or more radiology signs was specific for grade 1 neoplasms. RAS7 ≥1 (cut off 0.5) was 73.7% sensitive and 90% specific while RAS9 ≥1 (cut off 0.5) was 73.7% sensitive and 100% specific for diagnosing grade 1 neoplasms.
In long bone primary chondroid neoplasms at SUVMax cut-off 3.65. Mean SUVMax for grade 1 lesions was 3.42 (range 1.3 to 7.5) and the IHGCS mean SUVMax was 4.92 (range 2.3 to 11.3). The presence of 4 or more radiology signs was suggestive for IHGCS neoplasms. RAS7 ≥4 (cut off 3.5) was 90% sensitive and 61.3% specific while RAS9 ≥4 (cut off 3.5) was 70% sensitive and 71% specific for diagnosing IHGCS neoplasms from grade 1 neoplasms.
SUVMax was extremely useful in differentiating low grade (grade 1) chondrosarcomas from secondary chondrosarcomas in the absence of classical radiology features with the underlying presence of osteochondromas or Ollier disease. SUVMax cut-off was 3.65 (AUC =.896, 100% sensitivity and 75% specificity).
SUVMax obtained from 18F-FDG PET/CT is an excellent indicator for diagnosing dedifferentiated chondrosarcomas across all groups; overall cut off SUVMax 14.8 (87.5% sensitive and 100% specific). Radiology features and RAS7/RAS9 proved to be challenging due to the overlap of features across the IHGCS and dedifferentiated grades.

Conclusion: Tumor metabolic activity correlates with the histologic grade in chondroid neoplasms and the addition of 18F-FDG PET/CT with SUVMax cut off at 3.65 can aid in treatment planning by guiding us towards a low-grade neoplasm which may be dealt with intralesional extended curettage or high-grade lesion which need to be resected. Standalone SUVMax does not solve the dilemma of differentiating benign from low-grade chondroid neoplasms but may guide us towards a correlational diagnosis along with radiology and pathology.

			All (106)	Grade0 (25)	Grade1 (18)	IHGCS 2+3 (54)	Dediff (9)
Gender							
Male			68	12	13	37	6
Female			36	13	5	17	3
Age (Mean Years)			46.5	46.8 (15 to 69)	42.22 (13 to 69)	46.96 (14 to 74)	52 (38 to 72)
Tumor Location							
Spine			2			1	1
Sacrum			2		1	1	
Pelvis			24		3	18	3
Femur			35	8	7	16	4
Tibia			12	1	3	8	
Fibula			4	1	1	2	
Humerus			23	13	2	8	
Scapula			2		1	0	
Clavicle			2	2	0		
Tumor Size (Mean_cm)			8.21	4.7 (1.1 to 9.5)	7.24 (1.9 to 17.7)	9.53 (2.7 to 20)	12.01 (6.2 to 21)
SUVMax (Mean)			5.78	2.57 (0 to 4.3)	3.04 (1.3 to 7.5)	5.59 (2.3 to 13.3)	21.1 (7.6 to 38.4)
Radiology Features							
Medullary Expansion	RAS7	RAS9	49	1	11	32	5
Endosteal Scalloping ≥2/3rd Cortical thickness			24	4	3	15	2
Endosteal Scalloping ≥2/3rd lesion length			68	7	9	45	7
Cortical erosion/break			49	1	4	37	7
Soft tissue component			34		3	24	7
Periosteal reaction			34	2	4	22	6
Pathological fracture			5			5	
Cortical thickening			6			6	
Edema			39	1	4	26	8
RAS7 (Median)			3	0	2	4	4
RAS9 (Median)			3	0	2	4	5

Image 2: High AUC for SUVMax cut off at 3.65 to differentiate between Grade1 and Higher Grade (Grade 2 and 3) Chondrosarcomas

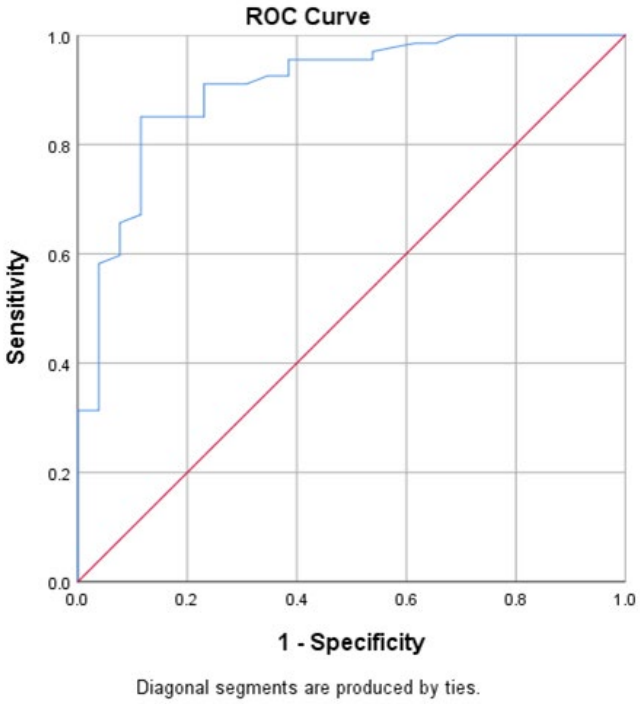
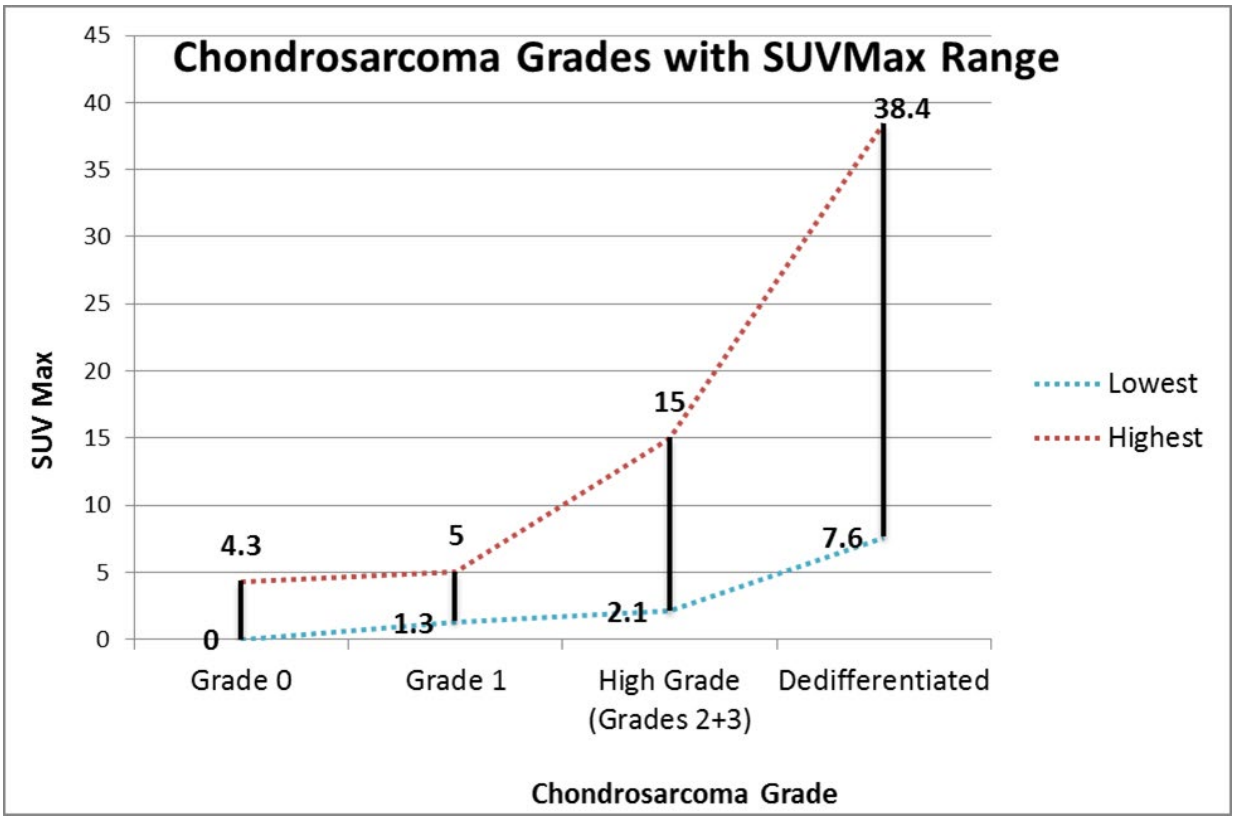


Image 3: SUVMax values for various grades of Chondrosarcomas



Poster #113 3461875

CLINICOPATHOLOGICAL FEATURES AND TREATMENT OUTCOME OF OESOPHAGEAL GASTROINTESTINAL STROMAL TUMOUR (GIST): A LARGE, RETROSPECTIVE MULTICENTER EUROPEAN STUDY

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Objective: Gastrointestinal stromal tumours (GISTs) arising in the oesophagus account for 1% of all GIST cases, and therefore evidence to guide decisions is limited. We performed a multicenter, international, retrospective study to investigate the clinicopathological features of oesophageal GIST in relation to treatment outcome.

Methods: Patients with primary oesophageal GIST from seven European countries, diagnosed between 2000 and 2019, were included. Clinicopathological features and outcome of (neo)adjuvant and endoscopic and surgical treatments are described. By using the Kaplan-Meier method, recurrence free survival (RFS) and disease-free survival (DFS) were estimated. To identify potential prognostic factors, multivariable Cox regression analysis was performed.

Results: Eighty-three patients (71.1% males) with oesophageal GIST were identified, with a median follow up duration of 55.0 months. At diagnosis, 59.0% had localized disease, 25.3% locally advanced and 13.3% presented with synchronous metastasis. Mutational analysis was available in 43 patients, with *KIT* exon 11 mutation present in 81.8%, *KIT* exon 13 in 1.2%, *KIT* exon 9 in 1.2%, and non-*KIT/PDGFRA* in 7.2% of cases. The mitotic count was classified as low (≤ 5 mitoses/50 high power fields) in 23 patients and high (> 5 mitoses) in 28 patients.
Fifty-one(61.4%) patients underwent surgical or endoscopic treatment and the most common reasons to not perform an immediate intervention (n=31) were; unresectable or metastasized oesophageal GIST, performance status/comorbidity , patient refusal or ongoing neo-adjuvant therapy. Twenty-three (39.7%) patients received neo-adjuvant imatinib therapy with median duration of treatment of 11.0 months (duration of treatment was available for 15 patients). A recurrence rate of 30.4% was observed among these patients. In patients treated with adjuvant imatinib therapy (n=11), 36.4% developed a recurrence during follow up.
The endoscopic intervention consisted of enucleation (n=11) and the two main types of surgical treatment were oesophagectomy with gastric conduit reconstruction (n= 33, 82.5%) and oesophagectomy without reconstruction (n=6, 15.0%). For one (2.5%) patient, the type of surgery was unknown. Two (18.2%) of patients treated with enucleation developed recurrent disease during a median follow up of 85.0 months. The local and distant recurrence rate in patients undergoing oesophagectomy with gastric conduit reconstruction was 6.1% (n=2) and 30.3% (n=10), respectively. In patients treated with oesophagectomy without reconstruction no local recurrence was observed while 16.7% had distant recurrence. Patients treated with enucleation had a median tumour size of 3.3 cm (range 2.2 cm- 6.0 cm) while patients undergoing oesophagectomy had a median tumour size of 7.0 cm (range 3.9 cm-20.0 cm). Larger tumours (4.0 cm and larger) had worse DFS than smaller ones. A median DFS of 84 months was observed for patients with tumours larger than 4,0 cm, while median DFS for tumours for smaller tumours was not reached (p=0.03). High mitotic count had similar effect on DFS (p=0.01) as patients with high mitotic count showed a median DFS of 31 months, whereas the median was not reached in patients with low mitotic count. Multivariable analysis did not reveal any independent prognostic factor for DFS.

Conclusion: This study comprises the largest retrospective cohort of oesophageal GIST patients with a detailed description of clinicopathological features and outcomes after treatment. Identical to gastric and small bowel GIST, tumour size and mitotic count were prognostic factors for DFS. Enucleation was used for smaller tumours and resulted in good outcomes. Based on these results, enucleation is recommended for tumours smaller than 3.0 cm while oesophagectomy should be reserved for larger tumours.

Poster #114 3461883

AVAPRITINIB VS REGORAFENIB IN PATIENTS WITH LOCALLY ADVANCED UNRESECTABLE OR METASTATIC GASTROINTESTINAL STROMAL TUMOR (GIST): EFFICACY AND SAFETY DATA FROM PHASE 3 VOYAGER STUDY

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Objective: Over 85% of GISTs harbor activating mutations in *KIT* or *PDGFRA*. Despite FDA approved second-, third- and fourth-line receptor tyrosine kinase inhibitors (TKIs), metastatic GIST remains incurable with median progression-free survival (PFS) of ≈6 months (mo) for therapies beyond imatinib. Avapritinib (ava) showed clinical activity in patients (pts) with active *KIT* and *PDGFRA* mutations in Phase 1 study NAVIGATOR, and was recently FDA approved for adults with unresectable or metastatic (U/M) GIST harboring a *PDGFRA* exon 18 mutation, including D842V mutations. VOYAGER assessed ava vs regorafenib (rego) in heavily pretreated U/M GIST.

Methods: VOYAGER was an open-label, randomized, Phase 3 study (NCT03465722) in pts with locally advanced U/M GIST previously treated with imatinib and 1 or 2 other TKIs. Pts with both *KIT* and *PDGRFA* wildtype tumors , or who received prior ava or rego, were excluded. Pts were randomized 1:1 to oral ava 300 mg once daily (QD) (continuous 28-day cycles) or oral rego 160 mg QD (3 weeks on/1 week off). Crossover from rego to ava was allowed for pts who experienced centrally confirmed disease progression. The primary endpoint was PFS per modified RECIST v1.1. Key secondary endpoints were objective response rate (ORR) per modified RECIST v1.1 and overall survival (OS); other secondary endpoints were disease control rate (DCR; defined as complete response [CR], partial response [PR], or stable disease [SD] for ≥4 cycles), duration of response (DOR), safety, and quality of life. Sample size of ≈230 pts per arm was designed for 90% power at 2-sided alpha of 0.05 assuming PFS hazard ratio (HR; ava vs rego) of 0.67.

Results: A total of 476 pts were enrolled to receive ava (n=240) or rego (n=236), of whom the majority had *KIT* mutations based on local testing, and 3% had *PDGFRA* D842V mutations. Median (range) age was 61 (31–91) years, 40% of pts were ≥65 years, 50% had ECOG PS of 1, and 67% were male. Primary endpoint of efficacy (improved PFS with ava) was not met, as there was no significant difference in PFS (HR 1.25; 95% CI 0.99–1.57) between ava and rego (4.2 mo vs 5.6 mo median PFS). Median DOR was 7.6 mo for ava and 9.4 mo for rego. Best ORR was 17% (all PR) for ava and 7% (all PR) for rego. DCR was 42% for ava and 46% for rego. With ava, 47% had SD and 28% had progressive disease (PD), and with rego 67% had SD and 21% had PD as best response. With ava, in pts who had *PDGFRA* exon 18-mutant GIST (n=11), ORR was 64% (all PR), 36% had SD, and no pts had PD as best response; for 7 of these pts who had D842V-mutant GIST, ORR was 43% (all PR), 57% had SD, and no pts had PD. In contrast, no pts with *PDGFRA* exon 18-mutant GIST (n=7, including 6 pts with D842V-mutant GIST) responded to rego (ORR 0%). Treatment-related adverse events (TRAEs) (any grade) occurring in ≥20% of pts in either arm (ava, rego) were: anemia (40%, 12%), nausea (39%, 15%), fatigue (35%, 34%), increased bilirubin (28%, 17%), periorbital edema (28%, 0%), face edema (27%, <1%), diarrhea (21%, 35%), decreased appetite (18%, 25%), hypertension (5%, 23%), dysphonia (3%, 28%), and palmar-plantar erythrodysesthesia syndrome (<1%, 59%). Cognitive effects (any grade) occurred in 26% of pts with ava and in 4% of pts with rego. Grade ≥3 cognitive effects occurred in 1%

with ava and 2% with rego. Intracranial bleeding of any grade occurred in 3 pts receiving ava (1%) and was grade ≥3 in 2 pts receiving ava (<1%); no pts in the rego arm experienced intracranial bleeding. The rates of discontinuation due to TRAEs were 9% with ava and 6% with rego.

Conclusion: Despite no statistically significant difference in PFS between study arms, the 17% ORR with 7.6 mo DOR in pts receiving ava was consistent with the ORR in the NAVIGATOR study, indicating that a subset of pts derive clinical benefit from ava. The AE profile of ava was similar to previous reports, importantly, the 26% cognitive effects rate was lower than the 41% reported in the NAVIGATOR study. AE profiles were distinct for ava and rego.

Poster #115 3462029

LAROTRECTINIB EFFICACY AND SAFETY IN PEDIATRIC PATIENTS WITH TRK FUSION SARCOMAS

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Objective: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a diverse range of tumor types. They are present in most infantile fibrosarcomas (IFS) and have also been detected in other pediatric sarcomas at lower frequencies. Larotrectinib, a highly selective and CNS-active tropomyosin receptor kinase (TRK) inhibitor approved by the FDA and EMA, demonstrated an objective response rate (ORR) of 79% and a median duration of response (DoR) of 35.2 months in 159 adult and pediatric patients with various cancers (Hong DS et al. *Lancet Oncol*. 2020). We report the activity and safety of larotrectinib in pediatric patients with TRK fusion sarcomas from an expanded dataset.

Methods: Pediatric patients <18 years old with RECIST-measurable sarcomas harboring *NTRK* gene fusions and treated with larotrectinib were identified from two clinical trials (NCT02576431, NCT02637687). Patients received larotrectinib 100 mg/m^2 (maximum dose of 100 mg) twice daily. Response was investigator assessed per RECIST v1.1.

Results: By July 15, 2019, 55 pediatric patients with TRK fusion sarcomas had been treated: 34 with IFS and 21 with other soft tissue sarcomas (spindle cell sarcoma [n=9], inflammatory myofibroblastic tumor [n=4], malignant peripheral nerve sheath tumor [n=2], not otherwise specified [n=2], and myofibromatosis, lipofibromatosis, myopericytoma, and small round cell tumor [each n=1]). Median age was 1.3 years (range 0.1–17.8); 8 (15%) patients were ≤3 months old. Overall, 37 (67%) and 18 (33%) patients had locally advanced and metastatic disease, respectively (in the IFS subgroup, 28 [82%] locally advanced and 6 [18%] metastatic). In total, 16 (29%) patients had not received prior systemic therapies while 18 (33%) had received ≥2 systemic therapies. ORR with larotrectinib for all patients was 93% (95% CI 82–98), 100% (95% CI 90–100) in patients with IFS, and 81% (95% CI 58–95) in patients with other soft tissue sarcomas (**Table**). The median time to response was 1.8 months (range 0.9–6.6). The median DoR, progression-free survival (PFS), and overall survival (OS) were not reached. The Kaplan–Meier estimate for the 12-month DoR was 89% (95% CI 73–96), 12-month PFS was 85% (95% CI 69–93), and 12-month OS was 95% (95% CI 81–99). Treatment duration ranged from 1.8+ to 38.6+ months. Fifteen patients, 12 of whom had locally advanced, previously unresectable disease, had tumor resection during treatment with 6 achieving a pathological complete response. Twelve patients stopped treatment after surgery; 3 patients received adjuvant therapy (≤3.1 months) prior to discontinuing. Thirty-four (62%) patients had Grade ≥3 treatment-emergent adverse events (AEs). AEs deemed related to larotrectinib were mostly Grade 1–2. Thirteen (24%) patients had Grade ≥3 larotrectinib-related AEs, and 1 patient discontinued treatment due to a larotrectinib-related AE (decreased neutrophil count).

Conclusion: Larotrectinib is highly active with a favorable safety profile in pediatric patients with TRK fusion sarcomas. These data strongly support testing for *NTRK* gene fusions in patients with sarcomas.

	IFS (n=34)	Other soft tissue sarcomas (n=21)	All pediatric sarcomas (n=55)
ORR, n (%)	34 (100)	17 (81)	51 (93)
Complete response	8 (24)	5 (24)	13 (24)
Pathological complete response	5 (15)	1 (5)	6 (11)
Partial response	21† (62)	11 (52)	32 (58)
Stable disease	0	3 (14)	3 (5)
Progressive disease	0	1 (5)	1 (2)

†Includes 2 patients with a partial response pending confirmation.
IFS, infantile fibrosarcoma; ORR, objective response rate.

Poster #116 3462147

MANAGEMENT OF HEMANGIOENDOTHELIOMA AT A DEDICATED SARCOMA CLINIC IN INDIA: TIME TO LOOK TOWARDS ANTI-ANGIOGENIC THERAPY

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Objective: Hemangioendothelioma is a locally aggressive, intermediate-grade tumor arising from the vascular endothelium. This tumor has multiple pathologic subtypes with a wide spectrum of presentations. Literature regarding management of advanced hemangioendothelioma is scarce, especially from the developing world. The available data predominantly comprises of studies on conventional chemotherapy-based regimens with limited insight on anti-angiogenic therapy. Our study offers the medical oncologists' perspective on management of hemangioendothelioma at a tertiary-care centre with focus on treatment modalities and outcomes.

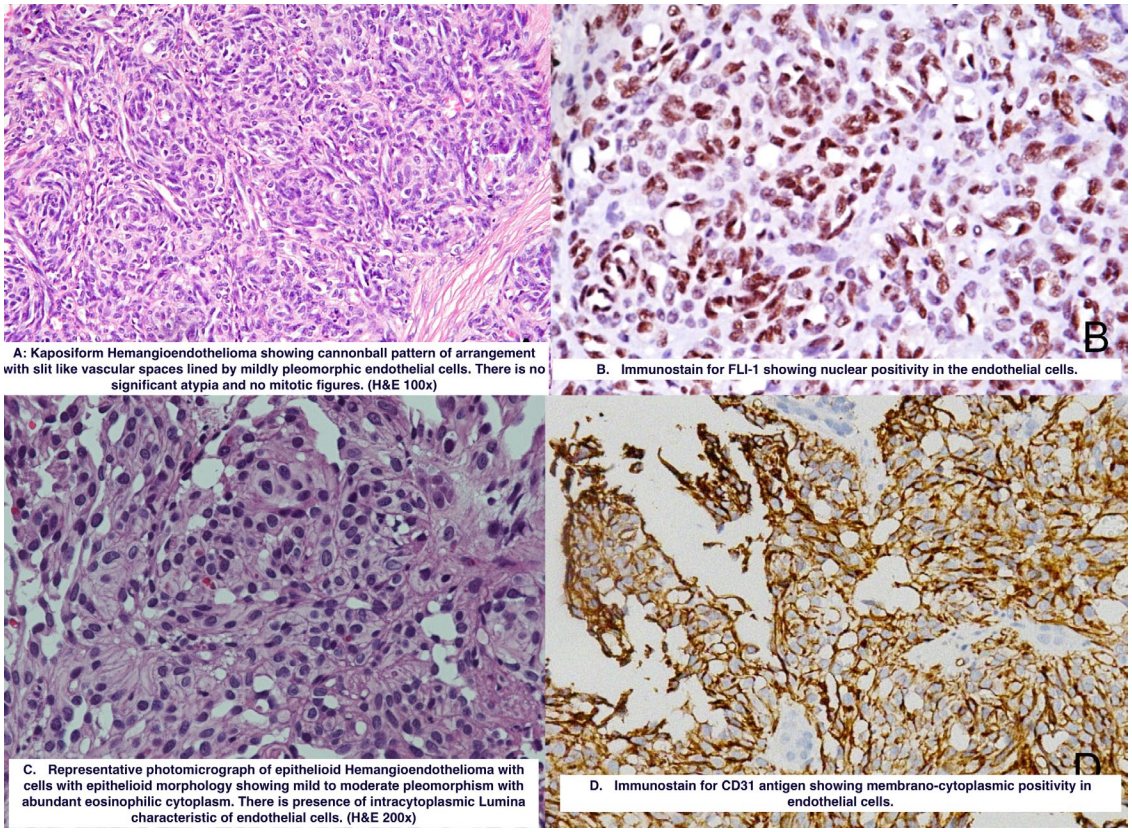
Methods: This is a retrospective study evaluating patients with localised or advanced hemangioendotheliomas registered in sarcoma medical oncology clinic between June 2015 and June 2020 with follow-up until June 2020. Pathology was reviewed by sarcoma pathologists and discussed in multidisciplinary clinics. Data was evaluated through hospital records including age, sex, primary site, metastatic sites, histopathology and IHC, therapy administered, response rate and outcomes. Statistical analysis was done through SPSS 23 (SPSS, Chicago, IL). Nominal data is provided as number (%) and continuous data as median and mean values as applicable. PFS was calculated from the date of initiation of treatment to the first date of documented progressive disease or death from any cause.

Results: The study included ten patients with median age of 34.5 years (4-60 years) comprising of nine males (90%) and one female (10%). Most common histology was epithelioid type in 70% (n=7) patients and kaposiform, pseudomyogenic and retiform types histology were 10% each. At the time of presentation to our center, the disease was metastatic in 70% (n=7), locally advanced in 20% (n=2), and 10% (n=1) had undergone excision surgery for localised disease. Bone and liver were the most common primary sites in 30% cases (n=3) and pain was the most common symptom. The most common sites of metastases were lymph nodes and bone (n=4 each), while liver was second (n=2). Epithelioid was the most common subtype (n=7), and kaposiform, retiform, pseudomyogenic were found in 1 patient each. Anti-angiogenic agents were used in 6 patients (66%) in 1st line and 4 patients (80%) in 2nd line. Conventional chemotherapy was given to patients requiring urgent response, namely spinal compression, impending hepatic rupture, bulky refractory disease and vision-threatening orbital metastases in 1 patient each. With first line anti-angiogenic therapy, there was complete remission in 14.2% (n=1), stable disease in 14.2% (n=1) and disease progression in 28.5% (n=2). With second line anti-angiogenic therapy, 40% (n=2) had partial response, 20% (n=1) had stable disease and 20% (n=1) had disease progression. All patients had disease progression with 1st line and 2nd line conventional chemotherapy. Overall, the mean PFS with 1st line medical therapy was 7.3 months (2.1-12.5 months) and 27.8 months (9.3-46.2 months) with 2nd line. Mean PFS with conventional chemotherapy was 1.6 months in 1st line (0.3-2.9 months) and 2 months in 2nd line respectively. With anti-angiogenic therapy, patients attained an impressive mean PFS of 10.4 months (3.6-17.2 months) in 1st line and 34.2 (16 to 52.4 months) months in the 2nd line. Median PFS was not reached in anti-angiogenic treatment. There was a single mortality and one patient was lost to follow-up.

Conclusion: Hemangioendothelioma is a vascular sarcoma with epithelioid hemangioendothelioma being the commonest subtype. While surgery is the treatment of choice for localised disease, choice of systemic therapy for advanced disease remains poorly defined. This disease is poorly responsive to conventional chemotherapy with better outcomes with anti-angiogenic therapy in first-line and relapsed settings. This study provides a glimpse into the management of hemangioendothelioma, and our findings strongly support the use of anti-angiogenic therapies in the current times.

Clinical and histopathological details of patients

S. no.	Age (years)/ sex	Presenting symptoms	Primary site	Disease status at presentation	Metastatic sites	Pathological subtype with IHC marker	
1	35/male	Shoulder pain	Upper extremity soft tissue	Locally advanced	Nil	Pseudomyogenic	CK, CD31, ERG
2	50/male	Lower limb swelling	Tibia	Localised	Nil	Epithelioid	N/A
3	4/male	Lower limb swelling with cutaneous lesions	Tibia	Locally advanced	Nil	Kaposiform	CD31, CD34, FLI-1
4	8/male	Acute paraparesis	Vertebra	Metastatic	Bone	Epithelioid	CD31, Vimentin
5	27/male	Pain abdomen	Spleen	Metastatic	Bone, lymph node, pancreas	Epithelioid	CD31, fVIII
6	60/male	Pain over lower back	Paravertebral soft tissue	Metastatic	Pleura, pleural fluid, lymph node	Epithelioid	CD31, CD34
7	34/male	Pain abdomen	Liver	Metastatic	rib, lymph node	Epithelioid	CD31, CD34, CD68, FLI-1
8	52/male	Pain abdomen (acute) with splenic rupture	Spleen	Metastatic	Liver, vertebra	Retiform	CD31, FLI-1
9	15/male	Asymptomatic	Spleen	Metastatic	Liver, lung	Epithelioid	CD31, FLI-1
10	49/female	Pain abdomen	Liver	Metastatic	Lymph node	Epithelioid	CD31, CD34 fVIII



A: Kaposiform Hemangioendothelioma showing cannonball pattern of arrangement with slit like vascular spaces lined by mildly pleomorphic endothelial cells. There is no significant atypia and no mitotic figures. (H&E 100x)

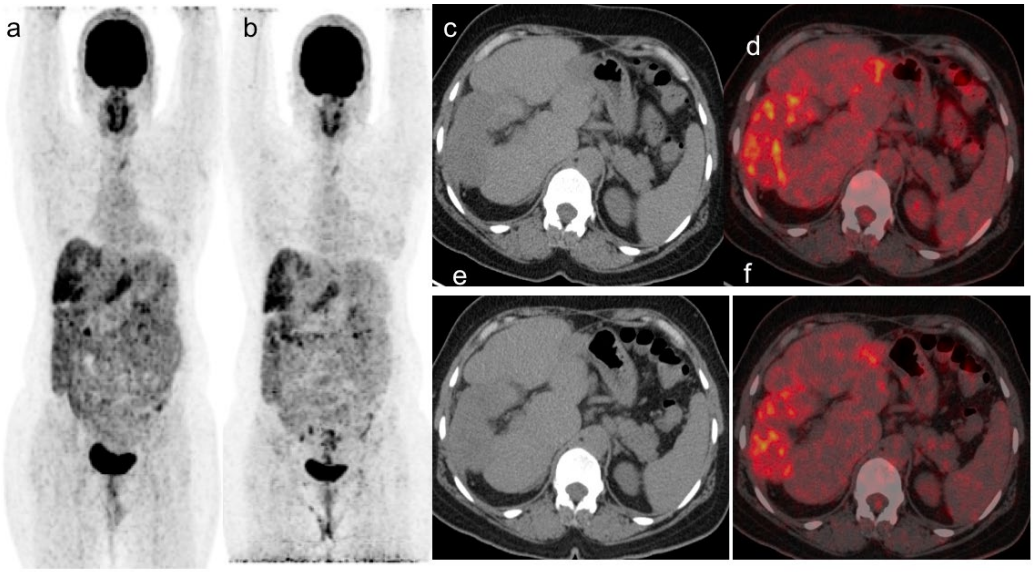
B. Immunostain for FLI-1 showing nuclear positivity in the endothelial cells.

C. Representative photomicrograph of epithelioid Hemangioendothelioma with cells with epithelioid morphology showing mild to moderate pleomorphism with abundant eosinophilic cytoplasm. There is presence of intracytoplasmic Lumina characteristic of endothelial cells. (H&E 200x)

D. Immunostain for CD31 antigen showing membrano-cytoplasmic positivity in endothelial cells.

Management details of patients under study

S. no.	Type of surgery	1st line medical treatment	Progression-free interval (months)	Best response	2nd line medical treatment	Progression-free interval (months)	Best response	Current status
1.	Multiple debulking surgeries	Pazopanib	1.5	Progressive disease	Doxorubicin	2	Progressive disease	Alive, on best supportive care
2.	Definitive excision	None	27	Complete remission				Lost to follow-up since 2 years
3.	Debulking surgery	Propranolol	17	Complete remission				Alive, on therapy
4.	Laminectomy	Vinblastine	1	Progressive disease	Sorafenib propranolol	5	Stable disease	Alive, on therapy
5.	None	Pazopanib propranolol	1	Not evaluated				
6.	None	Gemcitabine paclitaxel	1	Progressive disease	Pazopanib	2	Partial response	Alive, on therapy
7.	Hepatectomy + Liver transplant + Metastatec-tomy	Sorafenib Propranolol	17	Stable dis-ease				Alive, on therapy
8.	Splenectomy	Gemcitabine Paclitaxel	3	Progressive disease	Pazopanib	2	Progressive disease	Expired
9.	None	Pazopanib	2	Not yet evaluated				Alive, on therapy
10.	None	Thalidomide Celecoxib	4	Progressive disease	Pazopanib	45	Partial response	Alive, on therapy



a – Maximum intensity projection image of FDG PET- CT showing increased tracer uptake in the liver
b - Maximum intensity projection image of follow-up FDG PET- CT showing increased tracer uptake in the liver
c & **e** - CT section of the abdomen showing irregular contour of the liver showing multiple hypodense lesions in both the lobes of liver of pre and follow up scans showing Increased FDG uptake in the fused PET-CT scans (**d&f**)

Poster #117 3462149

MODELING THE EFFICACY OF NY-ESO-1 TCR T CELLS (LETETRESGENE AUTOLEUCEL; GSK3377794) IN PATIENTS WITH SYNOVIAL SARCOMA: CORRELATIONS OF RESPONSE WITH TRANSDUCED CELL KINETICS AND BIOMARKERS

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Objective: NY-ESO-1–specific T cells (letetresgene autoleucel, abbreviated to lete-cel; GSK3377794) are autologous CD4+ and CD8+ T cells transduced to express a high affinity T-cell receptor capable of recognizing NY-ESO-1 antigen in complex with HLA-A2. NY-ESO-1 is a cancer testis antigen that is expressed in many cancers including high expression in synovial sarcoma. Study 208466 (NCT01343043) is a Phase I clinical trial, which assessed the safety and efficacy of lete-cel in patients with advanced synovial sarcoma. The trial included 4 cohorts with varying levels of antigen expression and lymphodepletion regimens (LDR) (**Table 1**). Safety and efficacy results for this trial are presented in a complementary abstract. This abstract presents the results of two complementary analyses: relation between transduced cell kinetics and treatment efficacy (exposure–response), and correlations of biomarkers with response.

Methods: Patients with unresectable, metastatic, or recurrent synovial sarcoma were enrolled to cohorts based on NY-ESO-1 tumor expression level and received lymphodepleting chemotherapy consisting of various regimens of fludarabine and/or cyclophosphamide prior to lete-cel infusion (n=45) (**Table 1**). Response was assessed per RECIST v1.1. Cell kinetics or persistence of transduced cells in the peripheral blood were measured by quantitative PCR of transgene vector copies in DNA extracted from peripheral blood mononuclear cells. Concentration of serum cytokines was measured by Meso Scale Discovery (MSD) immunoassay. Gene expression within tumor biopsies was evaluated by Nanostring. Post-hoc relationships between persistence, biomarker expression, and efficacy were evaluated in a hypothesis-driven manner using logistic and linear regression. Potential determinants (including cell dose, demographics, and NY-ESO-1 expression) of peak persistence and clinical response were tested using generalized linear models.

Results: Higher peak persistence (Pmax) was associated (p=0.012) with response (yes = PR or CR, no = SD or PD) across cohorts. A higher weight-normalized cell dose (p=0.00421) and high LDR (p=0.000910) were found to be associated with Pmax according to the generalized linear model: Pmax ~ cell dose + LDR. These relationships allowed for accurate retrospective prediction of probability of response from weight, cell dose, and LDR. Low LDR resulted in higher endogenous lymphocyte counts on the day of dosing, which trended with lack of response within and across cohorts. While the impact of fludarabine on IL-15 levels has been previously reported, data presented here show a novel, positive correlation between IL-15 levels pre-infusion and response (p=0.0332). Post lete-cel infusion, the concentrations of IFNγ, IL-6, and IL-2RA within the first week were significantly increased in responders as compared with non-responders. The peak expression of IL-2RA within the first week showed a linear correlation to Pmax. Gene expression analysis from 10 pre-treatment biopsies showed good correlation between NY-ESO-1 mRNA and protein expression measured by immunohistochemistry.

Conclusion: Exposure–response analysis of study 208466 reveals that efficacy appears to be driven by weight-normalized cell dose and LDR via Pmax. Biomarker correlation analysis indicates that LDR impacts the level of IL-15 pre-infusion, which correlates with response directly. Post infusion of lete-cel, IFN, IL-6, and IL-2RA levels appear to be promising pharmacodynamic markers. Optimizing dose and LDR may offer opportunities to maximize antitumor efficacy in individual patients and across populations.

Funding: GSK (study 208466; NCT01343043)

Table 1. NY-ESO-1 expression, lymphodepletion regimen, overall response rate, mean transduced cell dose, and mean peak persistence in Cohorts 1–4

Cohort N	NY-ESO-1 Expression	Lymphodepletion Regimen	Response Rate (%)	Mean Transduced Cell Dose in Billions (Min, Max)	Mean (Std. Dev.) Peak Persistence (vector copies/µg DNA)
Cohort 1 N=12	**High** IHC score 2+ or 3+ in ≥50% of tumor cells	**High LDR:** Fludarabine: 30 mg/m^2 IV Days –5 to –2 Cyclophosphamide: 1800 mg/m^2 IV on Days –3 and –2	6/12 (50%)	4.95 (0.451, 14.4)	76,800 (53,500)
Cohort 2 N=13	**Low** IHC score ≥1+ in ≥1% cells but not exceeding 2+ or 3+ in ≥50% cells	**High LDR:** Fludarabine: 30 mg/m^2 IV Days –5 to –2 Cyclophosphamide: 1800 mg/m^2 IV on Days –3 and –2	4/13 (31%)	2.81 (1.60, 5.01)	82,200 (53,600)
Cohort 3 N=5	**High** IHC score 2+ or 3+ in ≥50% of tumor cells	**Low LDR:** Cyclophosphamide: 1800 mg/m^2 IV on Days –3 and –2	1/5 (20%)	3.23 (1.53, 5.00)	41,000 (55,000)
Cohort 4 N=15	**High** IHC score 2+ or 3+ in ≥50% of tumor cells	**Low LDR:** Fludarabine: 30 mg/m^2 IV on Days –7 to –5 Cyclophosphamide: 600 mg/m^2 IV on Days –7 to –5	4/15 (27%)	2.67 (1.00, 4.95)	34,800 (41,100)

IHC, immunohistochemistry; IV, intravenous; LDR, lymphodepletion regimen.

Poster #118 3462192

CAN PATIENTS AT HIGH RISK FOR R2 RESECTION OF RETROPERITONEAL SARCOMA (RPS) BE IDENTIFIED PREOPERATIVELY?

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Objective: Grossly incomplete (R2) resection of RPS is rarely undertaken with planned palliative intent. R2 resection typically results from unexpected intraoperative findings, and portends poor survival. We seek to determine whether unplanned R2 resection can be predicted, and here investigate the utility of a machine learning–based approach to modeling this event using a robust multi-institutional dataset.

Methods: Consecutive patients who underwent resection of non-metastatic primary RPS at 9 sarcoma referral centres between 2002 and 2017 were included. Patient-, tumour-, treatment- and outcome- related data were collated from each centre's prospective RPS database. The predictive model was constructed by logistic regression with lasso regularization to minimize overfitting in view of the low rate of R2 resection (lasso regression). The dataset was split into a training cohort (histologic subtype and grade derived from resection specimen) and a test cohort (histologic subtype and grade derived from diagnostic preoperative biopsy). Minimal lambda was calculated using standard 10-fold cross-validation to limit out-of-sample error. All analyses were performed in R version 3.6.3 using the glm-net package.

Results: Out of a total of 1893 patients who underwent resection of primary RPS over a 15-year interval, 76 (4%) had an unplanned R2 resection. In order to develop an instrument to predict R2 resection, 1403 patients were included in the training cohort used to create the predictive model, and 413 patients were included in the test cohort to validate the model using only preoperatively available data. 70 patients with missing variables were excluded from analysis. Following multivariable analysis of association with R2 status in the training cohort, variables included in the final lasso regression machine-learning based model were age, tumour size, tumour FNCLCC grade (1 vs 2/3), histologic subtype (other vs DD-LPS) and multifocality (no vs yes). When applied to the test cohort, the model had an overall accuracy of 0.79 [95% CI : (0.7442, 0.8254)] in predicting actual R2 resection; C-index was 0.714, sensitivity was 0.65 and specificity was 0.8. The performance of the model appeared unlikely to enhance preoperative decision-making based on clinical judgement. The poor transferability likely reflected under-grading on pre-operative biopsy: of 111 test cohort RPS scored as grade 1 on biopsy, 42 (38%) were upgraded to grade 2 or 3 upon analysis of the resected specimen.

Conclusion: At sarcoma reference centres, R2 resection of primary RPS is a relatively rare event that is associated with advanced patient age, large tumour size, high grade and multifocality. R2 resection is challenging to accurately model based on preoperatively available information. Efforts should be made to improve the accuracy of grading on pre-treatment biopsy, including by specific targeting of vascularized highly metabolic areas.

Poster #119 3462260

ADDED VALUE OF SURGICAL NAVIGATION FOR CHALLENGING INTRA-ABDOMINAL OR PELVIC SARCOMA

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Objective: Resection of (recurrent) intra-abdominal or pelvic soft tissue sarcomas (STS) can be challenging due to difficult locations, various critical anatomical structures, a narrow pelvic space and/or fibrotic tissue after pretreatment. The aim of this study was to assess whether electromagnetic surgical navigation can be of added value during these resections.

Methods: STS patients who were included in a prospective surgical navigation study with lower intra-abdominal or pelvic tumor locations scheduled for laparotomy were selected. A pre-operatively patient specific 3D roadmap was made, which was registered to the patient in the OR using an intraoperative CBCT scan and tracked using electromagnetic reference-markers. During the operation, an electromagnetic pointer was used for localization of the tumor and critical structures. Our primary endpoint was feasibility of the system, secondary outcomes were safety and usability. Usability of the navigation system was evaluated based on a survey including the System Usability Scale (SUS), filled out by the surgeons after the operations.

Results: Nine sarcoma patients with a total of 12 tumors were included. Histological diagnoses were dedifferentiated liposarcoma (3), gastro intestinal stroma cell tumor (GIST) (2), leiomyosarcoma, myxofibrosarcoma, malignant peripheral nerve sheath tumor (MPNST) and clear cell sarcoma (all 1). Median age at surgery was 63 years (56-72), median tumor size was 5.2 cm (2.4-10.4). In 7 out of 9 patients the surgical indication was locally recurrent sarcoma. In 3 out of 9 patients, neoadjuvant radiotherapy and in 3 other patients neoadjuvant systemic treatment preceded the surgery. Median shortest distance of the tumor(s) to arteries was 0.02 cm (0.00-1.86), to veins 0.23 cm (0.00-5.97), bone 0.88 cm (0.00-2.32) and ureters 0.71 cm (0.00-6.60). Despite these short distances, 89% of the resections resulted in R0 resections. Application of the navigation was successful in all the operations without technical or safety issues. Based on the survey, surgeons stated that navigation resulted in shorter surgery time and made the resections easier and potentially safer. SUS scores showed a high user-friendliness of the navigation system.

Conclusion: Electromagnetic navigation facilitates resections of challenging lower intra-abdominal or pelvic soft tissue sarcomas, and might be of added value.

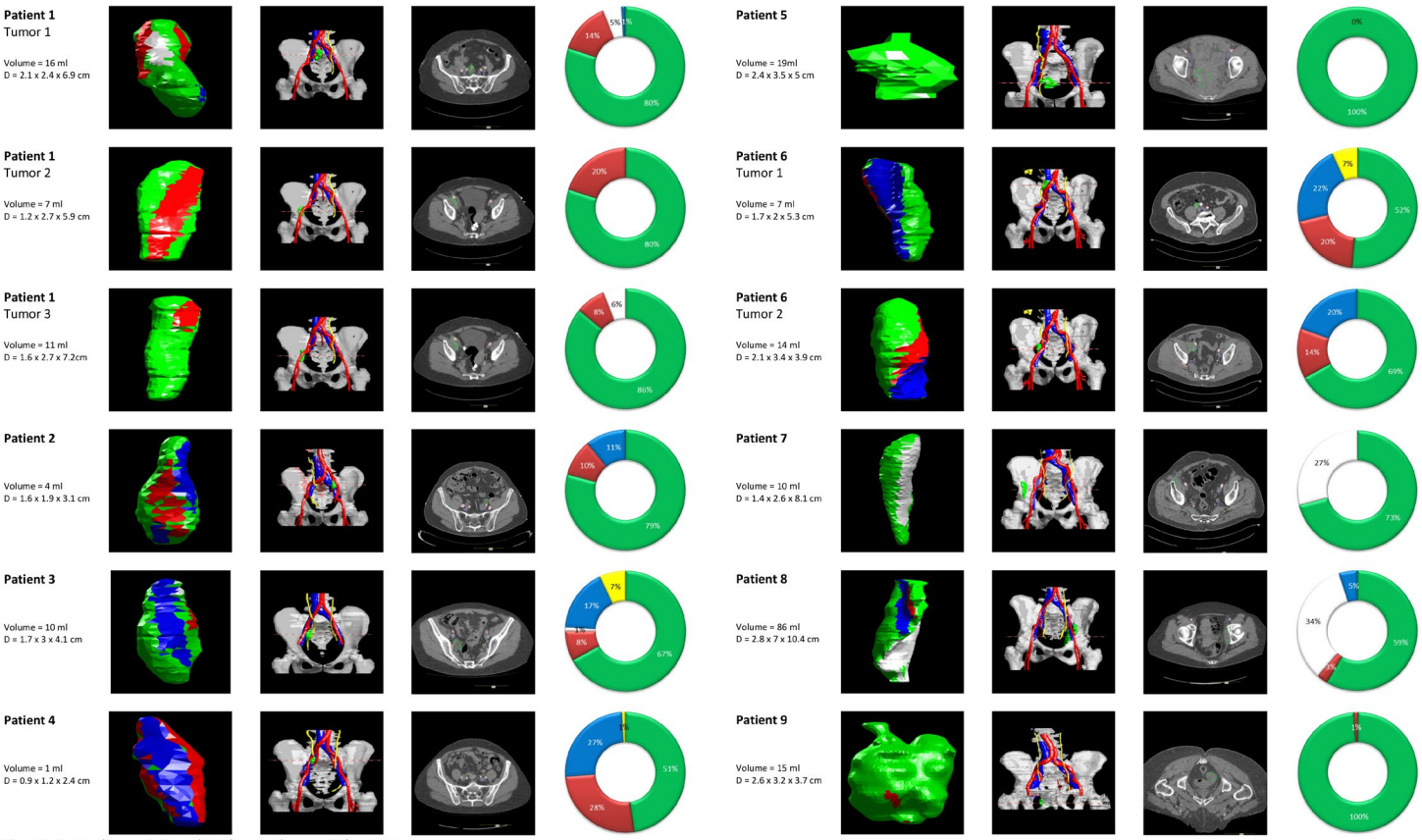

Figure 2. Tumor characteristics and nearby critical anatomical structures.
The images show a 3D model of each tumor, a 3D model of the tumors in relation to critical anatomical structures and a CT scan of the patient with tumor(s) and critical anatomical structures highlighted. The most right image shows which percentage of tumor surface is 'at risk', due to close related critical anatomical structures.
Tumor = green, artery = red, vein = blue, ureter = yellow, bone = white.

Poster #120 3462325

MANAGEMENT OF HIGH-GRADE EXTREMITY SOFT TISSUE SARCOMAS: AN EXPERT SURVEY

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Objective: The level of evidence for perioperative chemotherapy (CTx) for primary extremity soft tissue sarcoma (eSTS) is often debated, leading to distinct treatment protocols. Also, in spite of the availability of clinical guidelines, some studies showed variation in perioperative radiotherapy (RTx) administration. Therefore, we aimed to assess factors influencing the variation in RTx and CTx administration and evaluated the importance of selected patient- and disease characteristics for the recommendation of perioperative treatment with RTx and CTx, in patients with primary high-grade eSTS

Methods: Members of specialty oncology societies with a self-declared interest in STS were sent a web-based 21-item survey about eSTS management. The survey concerned only primary resectable high-grade eSTS in adults (≥18 years).

Results: The survey was filled out by 318 physicians who met the inclusion criteria. Of the respondents, 43.9% was an orthopedic, 26.2% a medical, 23.1% a surgical and 6.9% a radiation oncologist. The vast majority of respondents was from Europe (44.9%), North America (32.4%) and Asia (15.6%).

Of the respondents, 49% treated their patients frequently (≥75%) with perioperative RTx. Eleven percent of the respondents treated less than 10% of their patients with perioperative RTx. RTx was less often offered in Asia (9.3% treated frequently) compared with North-America (64.4%, P <0.001) and Europe (54.1%, P<0.001). The most important characteristics factored in the decision making for RTx administration were margin achieved, grade and margins expected (resectability) (figure 1A).

Of the respondents, 7.5% treated their patients frequently (≥75%) with perioperative CTx. Twenty-nine percent of the respondents treated less than 10% of their patients with perioperative CTx. More than 60% did not feel that there is enough evidence for the use perioperative CTx in patients with primary high-grade eSTS. Mainly, orthopaedic (73.3%) and surgical (73.5%) oncologist did not feel that there is sufficient evidence compared with medical oncologist (37.5%; P<.001, P<.001, respectively). The most important characteristics factored in the decision making for CTx administration were histological subtype, grade and size (figure 1B).

Of the respondents, 41.6% and 37.6% would always consider perioperative CTx in patients with synovial sarcoma and adult rhabdomyosarcoma respectively. The respondents would consider perioperative CTx treatment the least for alveolar soft part sarcoma and epithelioid sarcoma.

Conclusion: Specialty and continent-associated variation exists in perioperative treatment administration in patients with primary high-grade eSTS. This study also reveals the most important patient- and disease characteristics on treatment recommendations and the variation in attitude towards CTx by physician specialty.

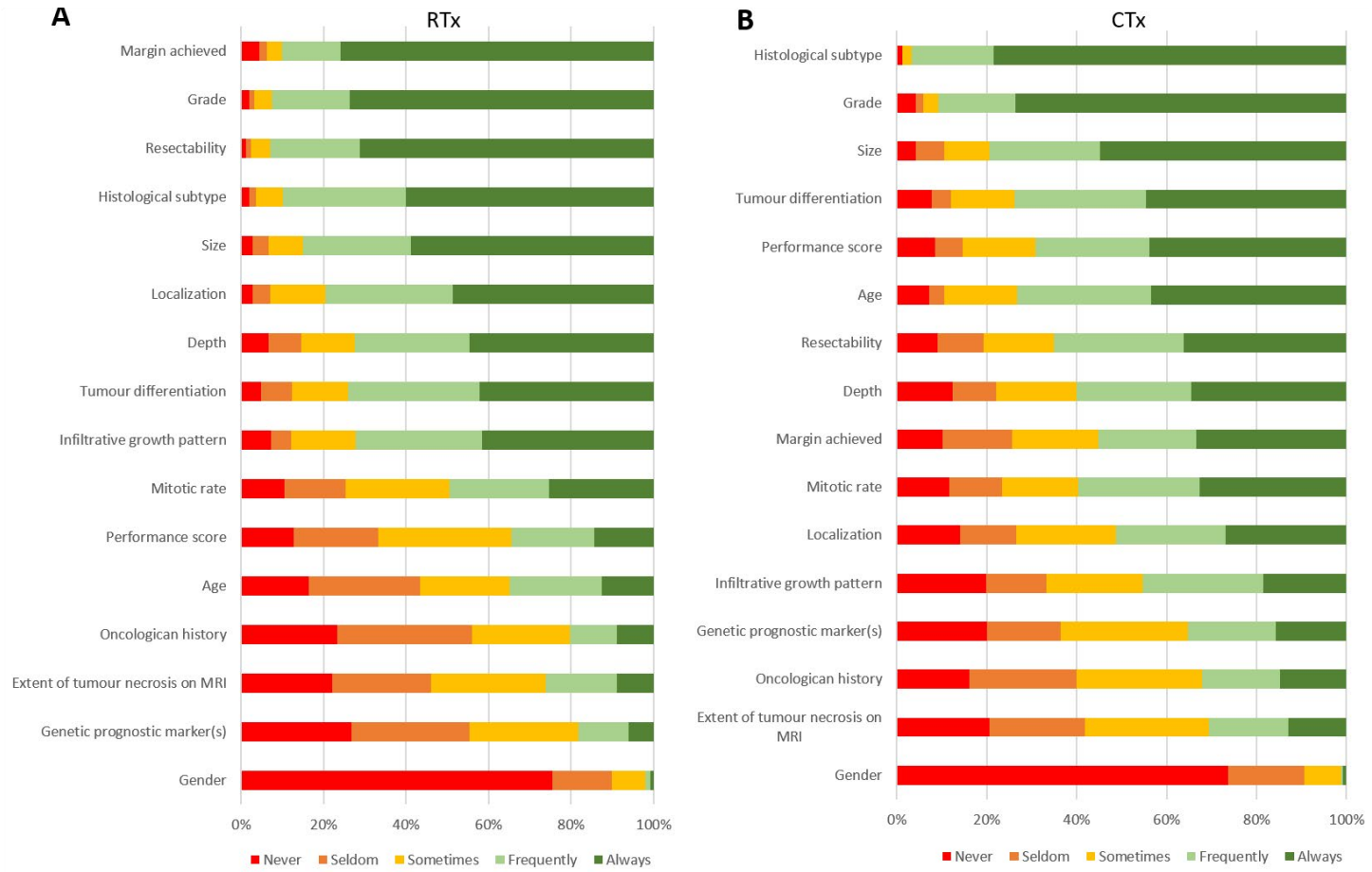

Figure 1A Importance of factors influencing RTx recommendation. Figure 1B Importance of factors influencing CTx recommendation.

Poster #121 3462376

COMPLETE PATHOLOGICAL RESPONSE TO NEOADJUVANT TREATMENT IS ASSOCIATED WITH BETTER SURVIVAL OUTCOMES IN PATIENTS WITH SOFT TISSUE SARCOMA

Sylvie Bonvalot[1], *Jay Wunder*[2], *Alessandro Gronchi*[3], *Javier Martin-Broto*[4], *Robert Turcotte*[5], *Marco Rastrelli*[6], *Zsuzsanna Papai*[7], *Stefano Radaelli*[3], *Lars Lindner*[8], *Felix Shumelinsky*[9], *Antonio Cubillo*[10], *Piotr Rutkowski*[11], *Danielle Strens*[12], *Clémentine Demaire*[12], *Georgi Nalbantov*[12]

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Objective: Localized soft tissue sarcoma (STS) management may include neoadjuvant treatment by radiotherapy (RT), chemotherapy (CT) or a combination of both (CRT) followed by a wide surgical excision. While pathological complete response (pCR) to preoperative treatment is prognostic for survival in osteosarcomas, its significance for STS is unclear. The aim of this study was to evaluate the prognostic significance of pCR to preop treatment on 3-year disease-free survival (3y-DFS) in STS patients.

Methods: This study is an observational, retrospective, international, chart review of adult patients with primary STS of the extremities and trunk wall, non-metastatic at diagnosis, any grade, diagnosed between 2008 and 2012, treated by at least surgery, and observed for a minimum of 3 years after diagnosis unless the patient died before. All histologic types were included except for the following: Kaposi's sarcoma, primitive neuroectodermal tumor, angiosarcoma, and epithelioid hemangioendothelioma. The primary objective was to evaluate the effect of pCR - defined as ≤ 5% viable tumor cells or ≥95% necrosis/fibrosis in the resected tumor- to preop treatment on 3y-DFS. DFS was defined as time between diagnosis to local or distant relapse or occurrence of other cancer or death, local recurrence-free survival (LRFS) as time between diagnosis and local relapse of the disease or other cancer or death, distant recurrence-free survival (MFS) time between diagnosis, and distant relapse of the disease or other cancer or death and overall survival (OS) as time between diagnosis and death of any cause. Statistical univariate analysis utilized chi-square independence test and odds ratio confidence interval (CI) estimation; multivariate analysis was performed using logistic LASSO regression.

Results: A total of 1066 patients' charts were reviewed. 330 patients treated by preoperative RT (67%), CT (15%) or CRT (18%) followed by surgery at 7 reference centers in 4 countries, who met all inclusion criteria and for whom pathological response was reported were included in the analysis (median age: 56 years old; range: 19-95). pCR was achieved in 22% of the patients (in 25%, 8% and 24% of the patients with preop RT, CT and CRT respectively). DFS at 3 years was observed in 76% versus 61% ($p<0.001$) of patients with and without pCR respectively. Multivariate analysis showed that pCR is associated with statistically significant higher chances of MFS (95% CI, 1.054-3.417; p=0.033), LRFS (95% CI, 1.226-5.916; p=0.014), DFS (95% CI, 1.165-4.040; p=0.015) and OS at 3 years (95% CI, 1.072-5.210; p=0.033).

Conclusion: This international multi-center study revealed that preop pCR increases the relative chance of 3y-DFS in a heterogenous STS population across different countries. Thus, pCR should be considered as a predictive factor of better survival outcomes in STS patients.

Poster #122 3462419

OVERALL SURVIVAL AFTER PERIOPERATIVE CHEMOTHERAPY IN THE MANAGEMENT OF PULMONARY METASTASIS IN OSTEOSARCOMA

Zeba Siddiqui[1], *Megan Delisle*[2], *Amirrtha Srikanthan*[3], *Ying Wang*[4]
[1]*Internal Medicine Residency Training Program, University of Ottawa, Ottawa, Ontario, CANADA;* [2]*General Surgery Residency Program Department, University of Manitoba, Winnipeg, Manitoba, CANADA;* [3]*The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, Ontario, CANADA;* [4]*BC Cancer Vancouver, University of British Columbia, Vancouver, British Columbia, CANADA*

Objective: Pulmonary metastasectomy is performed on a select cohort of patients with advanced osteosarcoma with the potential for long term survival. However, evidence on peri-operative chemotherapy at time of metastasectomy is not completely understood and difficult to summarize without a systematic examination of existing literature. The purpose of this project is to complete a pilot study to assess feasibility of a systematic review to summarize overall survival (OS) and prognostic factors in adults and children with advanced and recurrent osteosarcoma receiving chemotherapy around time of metastasectomy.

Methods: We performed a pilot review of survival studies conducted in children and adults with advanced and recurrent osteosarcoma who undergo pulmonary metastasectomy published in English with more than 5 patients. The primary outcome is overall survival. Literature searches were performed in multiple electronic databases including Ovid MEDLINE ® (1946 to present), Ovid EMBASE (1974 to present), Web of Science, and Cochrane Library. Two investigators independently screened all citations, abstracts, and full-text articles.

Results: 5 out of 33 observational studies between 1988 to 2017 were included in this pilot study, including a total of 419 who patients received perioperative chemotherapy around time of metastasectomy (Figure). No randomized controlled trials were identified. Studies included patients from China, Europe, and North America. The median OS ranged between 20 to 90 months (Table). Factors associated with survival include: age, number of lesions, disease free interval and laterality of pulmonary disease. Briccoli *et al.* found that chemotherapy administered after relapses did not have a significant effect on survival. Quality of life data was not available in the articles assessed.

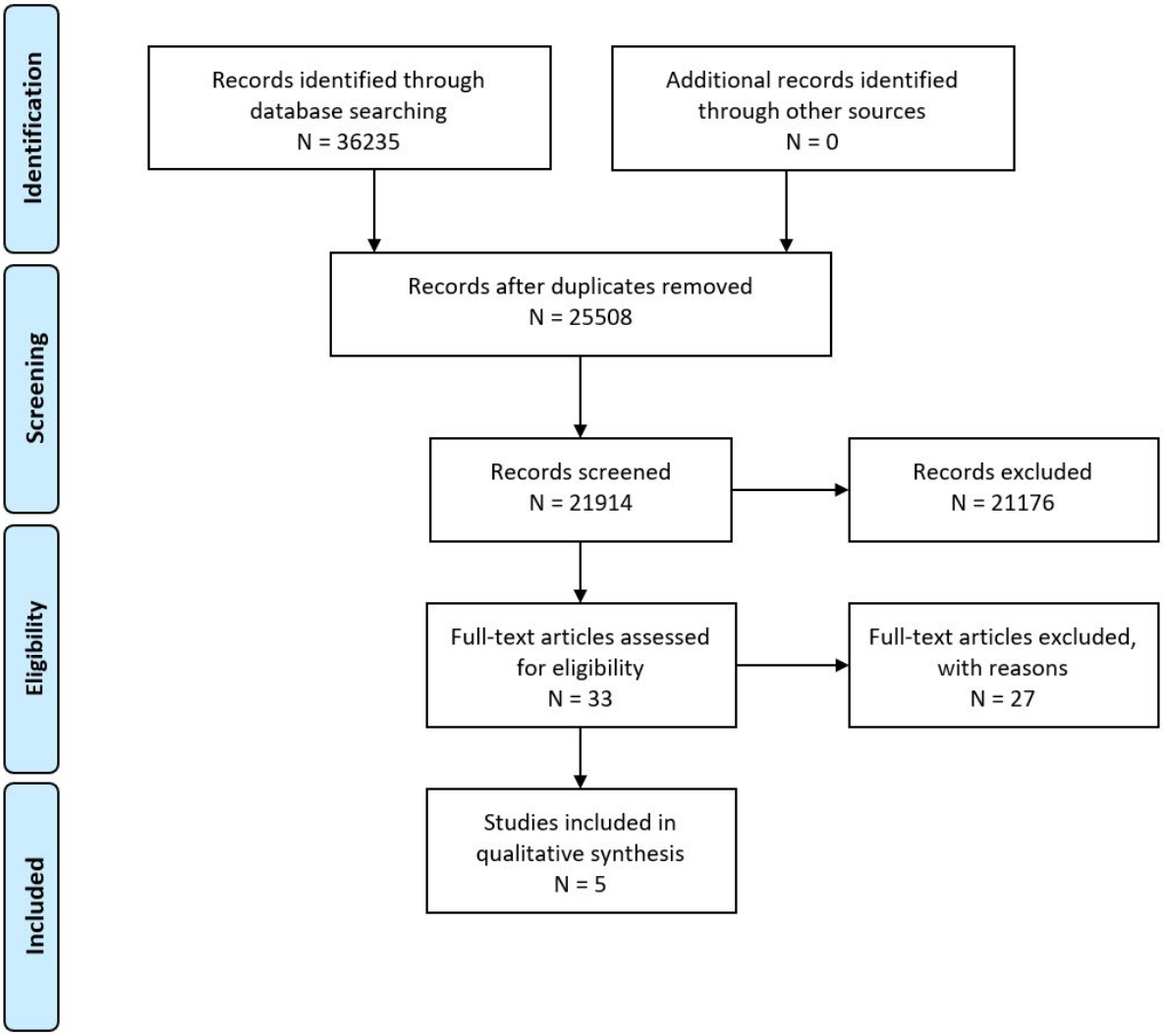
Conclusion: Overall survival in our pilot study has a significant range demonstrating the need for further investigation with a systematic review and meta-analysis. The main limitations are related to the inherently low-quality evidence as a result of lack of randomized controlled trials in this area. The current pilot study demonstrates reasonable data to proceed with full systematic review. Given the lack of equipoise, it is unlikely randomized controlled trials will be feasible. Thus, more comprehensive data is needed to guide shared decision making in this area.

Table: Medial overall survival of patients undergoing perioperative chemotherapy

Author, Year	No. of patients	Age (years)	Median OS (months)	3 year OS (%)	4 year OS (%)	5 year OS (%)
Al-Jilaihawi, 1988	23	15.6 (8 – 27)	-	45	39	-
Yu, 2017	40	28 patients more than 18 years, 12 patients under 18 years	20	-	32.5	-
Hawkins, 2003	15	15.3 (4.5 – 23)*	-	-	13	-
Briccoli, 2009	323	16 (4-55)	-	-	-	37
Durnali, 2016	18	19 (14-74)*	90 (7.2 – 172.9)	-	-	-

* value refers to median age of all patients included in the study

Figure: 5 out of 33 eligible studies were included in this pilot study



Poster #123 3462424

PRECLINICAL ASSESSMENT AND ANALYSIS OF ANTI-SEMA4D TREATMENT FOR OSTEOSARCOMA

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Objective: Osteosarcoma is the most common primary malignancy of bone and is most commonly diagnosed in children and teens. Despite advances in chemotherapy regimens, radiation therapy, and surgical resection, survival rates for osteosarcoma patients have not improved in more than forty years. While immunotherapy has shown promise in other cancer types, this therapeutic approach remains relatively unexplored for targeting osteosarcoma. Interestingly, semaphorin type IV D (SEMA4D) and its cognate PLXNB family receptors are endogenously expressed at high levels in many human solid tumor types including breast, colon, and ovarian cancer, and are commonly associated with poor patient prognoses. Our lab has previously shown that increased SEMA4D expression can mediate numerous oncogenic functions necessary for tumor growth, progression, and metastasis in osteosarcoma using the *Sleeping Beauty* (SB) mutagenesis system. Inhibiting SEMA4D-PLXNB receptor interactions represents a novel immunotherapeutic strategy to promote immune cell infiltration, reduce tumor progression, and decrease instances of tumor metastasis in SEMA4D^{+} osteosarcomas.

Methods: We treated immunocompromised and immunocompetent, orthotopic mouse models of osteosarcoma with either anti-SEMA4D (mAb67-2) or an isotype control. Beginning prior to cell engraftment, tumors were measured twice weekly until time of sacrifice. Tumors from both treatment groups were analyzed via flow cytometry and immunohistochemistry to evaluate for changes in immune cell populations. Tumor infiltrating lymphocytes were isolated from tumors and assayed by cytometric bead array (CBA) cytokine analysis to identify differences in cytotoxicity.

Results: Tumor measurements of both immunocompetent and immunocompromised animals suggest that anti-SEMA4D treatment induces a substantial anti-tumor response with a dramatic decrease in tumor volume in treated animals. Preliminary results indicate that there is increased immune cell infiltration of anti-SEMA4D treated tumors.

Conclusion: The reduced tumor progression is mediated, in part, through increased immune cell infiltration, enhanced T cell killing, and recruitment of pro-inflammatory immune cell populations. Additionally, reduced tumor progression is impacted by blocking SEMA4D-PLXNB receptor interactions, which inhibit oncogenic signals within the tumor microenvironment.

Poster #124 3462442

NCI PROTOCOL 10330: A PHASE 2 STUDY OF BELINOSTAT AND SGI-110 (GUADECITABINE) FOR THE TREATMENT OF UNRESECTABLE AND METASTATIC CONVENTIONAL CHONDROSARCOMA

Jay H. Oza[1], *Matthew Ingham*[1], *Shing Lee*[3], *Tahir Sheikh*[1], *Richard Piekarz*[2], *Gary Schwartz*[1]
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Objective: Conventional chondrosarcoma accounts for approximately 25% of primary bone cancers and is the second most common primary bone tumor after osteosarcoma. Surgical resection is the primary treatment for localized disease. In the unresectable or metastatic setting, chemotherapy has marginal efficacy with response rates of 12% or less. Currently, no FDA approved therapy exists for advanced chondrosarcoma. IDH1/2 mutation is seen in 50% of cases. Epigenetic dysregulation is central to oncogenesis in both IDH1/2 mutant and wild-type chondrosarcoma. Pre-clinical studies from our group show that combination treatment with HDAC and DNMT inhibitors is significantly more effective at suppressing the growth of chondrosarcoma models in vitro and in vivo compared to either therapy alone, regardless of IDH mutational status. These studies show that the combination regimen might mediate anti-tumor effects on chondrosarcoma by induction of apoptosis, inducing expression of tumor suppressor genes (eg. E-cadherin), the induction of interferon responsive genes (eg. IRF7, OASL, ISG15, DDX58) and reversal of global hypomethylated state. On the basis of these findings we have designed a phase 2 clinical trial with an HDAC inhibitor (belinostat) and a DNMT inhibitor (SGI-110, guadecitabine) in patients with unresectable or metastatic conventional chondrosarcoma.

Methods: NCI Protocol # 10330 is a single-arm, open-label, multi-center, Simon 2-stage phase 2 clinical trial evaluating belinostat and guadecitabine in patients with advanced conventional chondrosarcoma. Eligible patients will have locally advanced unresectable or metastatic (biopsy proven) conventional chondrosarcoma which is measurable by RECIST v1.1 and amenable to biopsy, ECOG PS ≤ 2, any number of prior treatments (including none). Patients will receive guadecitabine 45 mg/m^2 SC followed by belinostat 1000 mg/m^2 IV once daily on days 1-5 of a 28-day cycle. A safety lead-in and continuous toxicity monitoring rule will be applied. The primary endpoint will be objective response rate.

Because chemotherapy is associated with objective response rates of 8-12% in conventional chondrosarcoma and most clinical trials with targeted agents have shown response rates of 0%, we will consider an objective response rate of 8% as inactive while an objective response rate of 28% will suggest promising activity warranting further study. A Simon optimal 2-stage design is employed. The design calls for 26 patients. In stage one, 13 patients will be enrolled. If 2 or more responses are observed, the study will proceed to full accrual. If 5 or more responses are seen among 26 patients, the study treatment is considered promising. This design has 85% power with α of 0.054 to test for a response rate of 8% (null hypothesis) vs 28% (alternative hypothesis).

Secondary objectives include safety and tolerability and progression free survival (PFS). All patients will undergo pre-treatment and on-treatment (during cycle 2) tumor biopsies. Paired tissue will be used for correlative analysis including: 1) whole exome sequencing/RNAseq to evaluate changes in gene expression in response to treatment, 2) multiplex immunohistochemistry (mIHC) to interrogate the effect of combination therapy on tumor immune microenvironment and 3) a global DNA methylation assay to better understand the changes in epigenetic landscape in response to treatment. This study will be open throughout the ETCTN (NCT clinical trials # 04340843).

Results: Pending

Conclusion: Pending

Key Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Histologically confirmed conventional chondrosarcoma	Patients with dedifferentiated, mesenchymal or clear cell chondrosarcoma
Locally advanced unresectable or metastatic disease	Patients with any known UGT1A1 polymorphism, heterozygous or homozygous associated with reduced function
Measurable disease per RECIST v1.1 criteria and tumor site amenable to biopsy	Chronic use of any medications or substances that are strong inhibitors of UGT1A1
Any number of prior systemic chemo-therapy (including no prior therapy)	Pregnant women
ECOG PS ≤ 2, Karnofsky ≥ 60%	QTc ≥ 450 ms (after correction of any electrolyte abnormality)
Acceptable organ and marrow function	
Age ≥ 18 years	

Study Endpoints

Objective	Endpoint
Primary	- Objective response rate (ORR)
Secondary	- Toxicity profile of the combination treatment - Progression free survival (PFS)
Exploratory	- Evaluate for a relationship between the presence or absence of IDH1/2 mutation in a patient's tumor and clinical benefit from study treatment - To conduct RNAseq analysis using baseline and on-treatment tissue biopsies to study the effect of study treatment on gene expression patterns and identify candidate genes which may underline treatment efficacy - To evaluate for changes in global DNA methylation levels using baseline and on-treatment biopsies and correlate changes in global methylation with clinical benefit from study treatment - To use multiplex immunohistochemistry (mIHC) to interrogate the immune microenvironment in base-line and on-treatment tissue biopsies to define changes in infiltrating immune cell subsets and PD-L1/ MHC expression by immune and tumor cells associated with study treatment

Figure 1. SGI-110 (guadecitabine, DNMTi) and belinostat (HDACi) combination treatment demonstrates significantly greater anti-proliferative effect than either monotherapy. Chondrosarcoma cell lines were treated with no drug (ND), belinostat 300 nM daily, SGI-110 250 nM daily or the combination for 6 days and cell viability was assessed. CH2879 – IDH wt, JJ102 – IDH1 mut, CS1 & SW1353 – IDH2 mut.

Unpublished preclinical data from Schwartz Lab, CUIMC (manuscript in preparation)

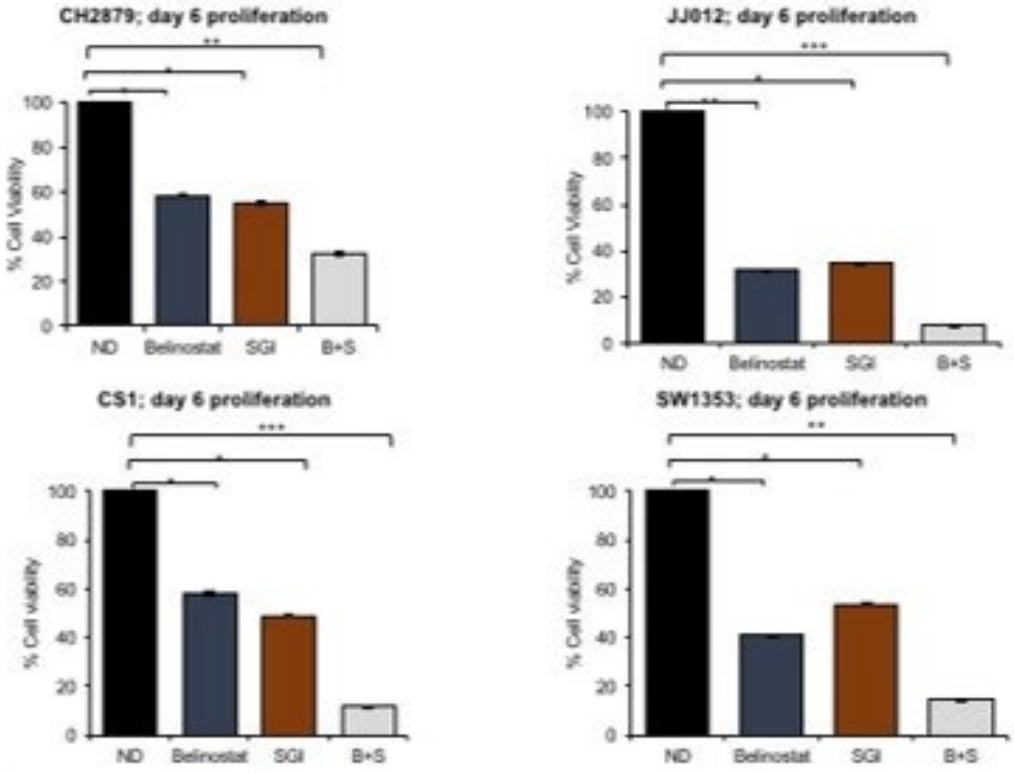


Figure 2. Combination treatment with 5-azacitidine (5-AZA, DNMTi) and vorinostat (SAHA, HDACi) induces significantly greater suppression of tumor growth than either monotherapy *in vivo*. Tumor growth of JJ-012 mouse xenografts treated with indicated drugs is shown. Treatment was started on day 38.

Unpublished preclinical data from Schwartz Lab, CUIMC (manuscript in preparation)

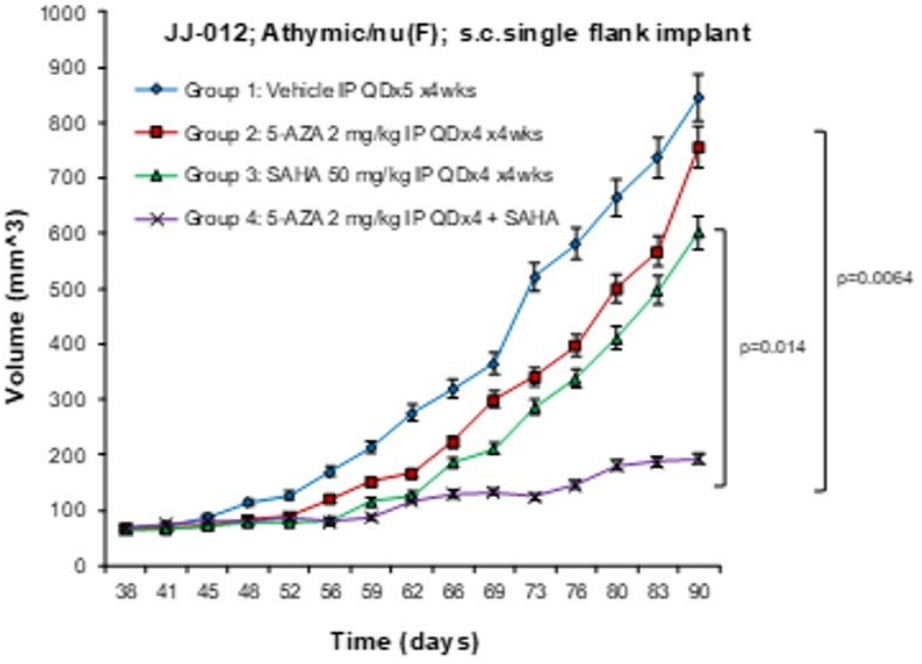
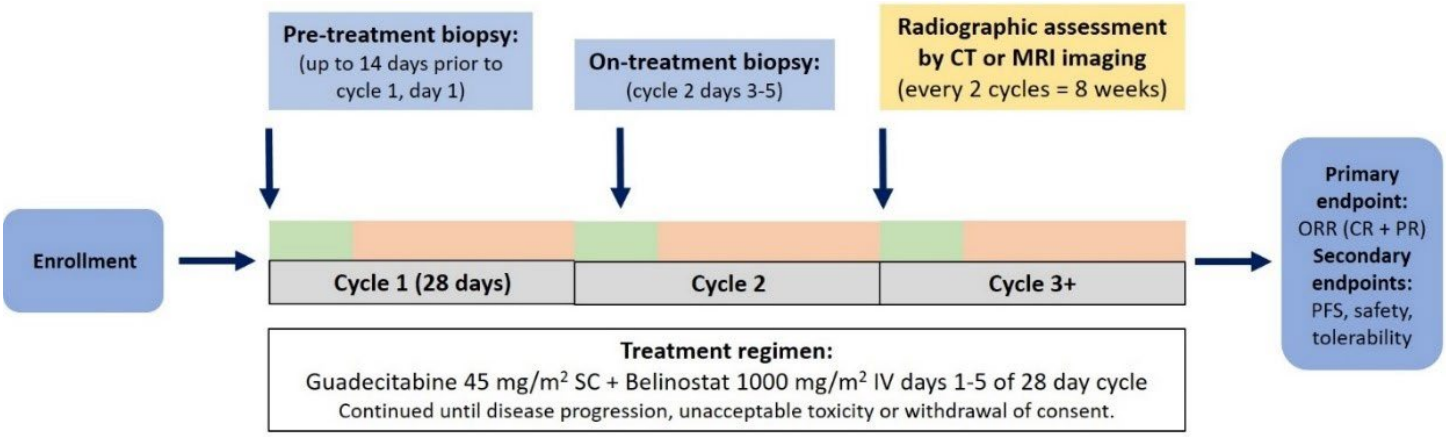


Figure 3. Study schema.



Poster #125 3462457

D-3-PHOSPHOGLYCERATE DEHYDROGENASE (PHGDH) INHIBITION DRIVES PRO-SURVIVAL MTOR DEPENDENCY IN OSTEOSARCOMA

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Objective: Osteosarcoma (OS) is the most common type of primary malignant bone tumor. Current treatment uses high-dose methotrexate (HD-MTX), which targets the folate pathway by inhibiting dihydrofolate reductase, as part of a pathway that converts serine to purines and thymidylate. We hypothesized that inhibition of PHGDH, the first and rate-limiting step in serine biosynthesis, would be active for the treatment of OS.

Methods: Immunohistochemistry analysis of an OS TMA of 260 patients was performed in a blinded fashion and correlated to patient outcomes data. OS, breast cancer, mesenchymal stem cell (bone precursor cells) lines were treated with NCT-503, a small molecule PHGDH inhibitor. Cell growth and viability assays were conducted using red nuclear staining and YOYO-1 fluorescent probes. A series of metabolomic and lipidomic assays using Seahorse Metabolomics and capillary electrophoresis mass spectrometry were utilized to quantify mitochondrial activity, cellular lipid content, metabolite levels, and transcriptional changes in response to PHGDH inhibition. Lysosomal localization was qualified using LysoTracker Deep Red fluorescent probes. *In vivo* analyses were also conducted.

Results: We found that over 50 % of clinically annotated samples are high expressers of PHGDH (moderate to strong intensity) and have identified an inverse correlation between expression of PHGDH and poor relapse-free survival ($p < 0.006$), as well as decreased overall survival ($p < 0.016$). We demonstrated that PHGDH-high OS cell lines were susceptible to treatment with high-dose single agent NCT-503. Metabolomics analyses showed that a decrease in *de novo* serine biosynthesis resulted in a metabolic adaptation driving mitochondrial fuel utilization away from glucose and prompting an increase in lipid uptake. This shift caused metabolite accumulation that trigged the activation of the mTORC1 signaling pathway, sensitizing cells to certain non-rapalog mTORC1 inhibitors *in vitro* and *in vivo*.

Conclusion: We have identified high PHGDH as a poor prognostic marker in patients with OS. We have also found that OS cell lines have up-regulated serine biosynthesis pathways that are sensitive to PHGDH inhibition. Finally, we have characterized the metabolic adaptations leading to an mTORC1 response in OS cell lines treated with a PHGDH inhibitor, sensitizing cells to certain mTORC1 inhibitors. PHGDH thus serves as an attractive target for the future development of treatments in OS.

Poster #126 3462463

TARGETING PARACRINE FIBROBLASTIC NETWORKS IN GASTROINTESTINAL STROMAL TUMOR INHIBITS CANCER GROWTH AND METASTASIS

Hyunho Yoon[1], *Chih-Min Tang*[1], *Sudeep Banerjee*[2], *Mayra Yebra*[1], *Sangkyu Noh*[1], *Adam M. Burgoyne*[1], *Jorge De la Torre*[1], *Martina De Siena*[1], *Mengyuan Liu*[3], *Lilli Klug*[4], *Yoon Young Choi*[5], *Antonio Delgado*[1], *Zhiyong Wang*[5], *Randall P. French*[1], *Andrew M. Lowy*[1], *Ronald deMatteo*[3], *Michael Heinrich*[4], *Alfredo A. Molinolo*[5], *J. Silvio Gutkind*[5], *Olivier Harismendy*[5], *Jason K. Sicklick*[1]

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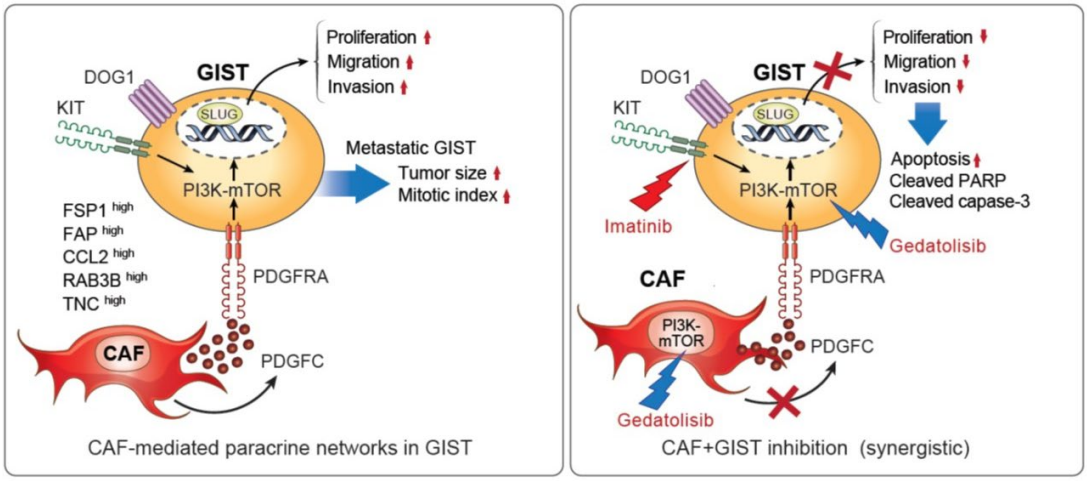
Objective: Gastrointestinal stromal tumor (GIST), which results oncogenic mutations in *KIT* and *PDGFRA* that can be specifically targeted, cannot be cured with chemotherapy alone. Here, we identify new molecular targets for GIST therapy by investigating the tumor microenvironment.

Methods: Primary cancer-associated fibroblasts (CAFs) were isolated from human GIST and characterized with GIST (*KIT*, *DOG1*) and CAF (*FAP, FSP1*) markers. We performed RNA sequencing analysis with GIST lines and CAFs to compare their gene expression patterns. Target gene knockdown in cells was performed using shRNA lentivirus. Knockdown levels were confirmed by qPCR, immunoblotting, and/or ELISA. *In vitro* cell viability, migration, and invasion assays were performed using co-culture and conditioned media. *In vivo* tumor metastasis, growth, and drug sensitivity of CAFs were performed and analyzed by histology.

Results: We identified a paracrine network by which CAFs drive GIST growth and metastasis. Specifically, CAFs isolated from human tumors were found to secrete high levels of PDGFC, and activation of PDGFRA signaling in neighboring GIST cells promoted tumor growth and metastasis. We also determined that these effects were regulated by expression of *SLUG* in tumor cells, which positively correlates with tumor size and mitotic index in metastatic GIST patients. Directly targeting the imatinib-resistant CAFs with a dual PI3K/mTOR inhibitor, gedatolisib, disrupted fibroblastic support and synergized with imatinib to increase *in vitro* tumor cell killing and *in vivo* disease response, thus identifying a previously unappreciated cellular target in GIST.

Conclusion: For the first time, we have demonstrated a novel role of CAF-mediated paracrine signaling in sarcoma progression. Our findings represent a paradigm shift for the sarcoma field, which has only focused on therapies directly aimed at killing tumor cells. These new findings suggest that non-cancerous mesenchymal cells within stromal tumors are may be critical for tumor growth and metastasis, as well as for improving treatment efficacy. Together, our work has therapeutic implications for clinical management of GIST, and immediate potential for translation into a clinical trial.



Poster #128 3462552

TP53 AS PROGNOSTIC MARKER IN PATIENTS WITH ADVANCED SARCOMA: A POOLED ANALYSIS OF MOSCATO AND PROFILER STUDIES

Elise Nassif[1], *Rastilav Bahleda*[1], *Edouard Auclin*[3], *Charles Honoré*[2], *Sarah Dumont*[2], *Mehdi Brahmi*[4], *Olivier Tredan*[4], *Olivier Mir*[2], *Isabelle Ray-Coquard*[4], *Axel Le Cesne*[2], *Jean-Yves Blay*[4], *Christophe Massard*[1], *Armelle Dufresne*[4]
[1]*DITEP, Institut Gustave Roussy, Paris, FRANCE;* [2]*Gustave Roussy, Villejuif, FRANCE;* [3]*APHP, Paris, FRANCE;* [4]*Centre Léon Bérard, Lyon, FRANCE*

Objective: Sarcomas are heterogeneous in their biology and clinical behavior. The aim of this study was to identify molecular alterations as prognostic or predictive of response to treatment for patients with advanced sarcomas.

Methods: Molecular profiles of patients included in two French multicentric prospective precision medicine clinical trials, MOSCATO and ProfiLER, were retrospectively analyzed. Clinical data of these patients were collected using the French Sarcoma Network national database, including major prognostic clinical and histological factors as well as treatment description in advanced setting. Next-Generation Sequencing was done on archived tissue or fresh tumor biopsy, when no archived tissue was available. Relevant molecular alterations were classified according to the published TCGA pathways and the three most frequently altered genes were selected for survival analysis. Each clinical data and molecular alteration was included in univariate model using log-rank test to seek for correlation with overall survival (OS), disease-free survival (DFS) and response to anthracyclines. Variables with $p < 0.05$ were subsequently incorporated in the multivariate analysis using Cox proportional hazard ratio.

Results: A total of 235 patients were included in this pooled analysis. Molecular analysis was done on primitive tumor tissue in 114 patients and on metastasis in 120 patients. The majority were soft-tissue sarcomas (STS) (74%, N=173), followed by bone sarcomas (20%, N=48) and GISTs (6%, N=14). In the STS cohort, the most represented histology were leiomyosarcomas (31%, N=53), rhabdomyosarcomas (16%, N=27), undifferentiated pleomorphic sarcomas (11%, N=20) and liposarcomas (10%, N=17). The three most frequently mutated genes were TP53 (23%), RB1 (12%) and CDKN2A (11%). The presence of TP53 mutation was significantly associated with worse outcomes in terms of DFS (HR= 1.57; 95%CI=1.1-2.25; p=0.01) in Cox model. Moreover, there was a trend for a worse OS from diagnosis when there were more mutations in the p53 pathway according to the TCGA.

Conclusion: A prognostic impact of TP53 mutations in patients with advanced sarcomas was suggested. These results warrant further confirmatory analysis on selected histologies. Sub-group analysis will be presented during the CTOS annual meeting, notably correlation between molecular alterations and response or resistance to anti-mitotic drugs. Moreover, detailed molecular data by histologic subtype will be further analyzed.

Poster #129 3462565

DIAGNOSTIC CHALLENGES OF INFANTILE SARCOMAS DRIVEN BY EGFR INTERNAL TANDEM DUPLICATIONS: A CASE SERIES

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Objective: To broaden the recognition of *EGFR*-altered infantile sarcomas and promote early sequencing via a description of case series and review of the literature.

Methods: Comprehensive genomic profiling included paired tumor/normal exome sequencing, targeted RNA sequencing, and whole transcriptome analysis of the disease-involved specimen.

Results: Patient 1 was diagnosed at birth with a large mass arising from the esophagus, causing airway compression and requiring a tracheostomy and gastrostomy. Biopsy at 3 weeks of age demonstrated a spindle cell tumor with few mitoses staining positively for SMA, vimentin, CD99, partial CD68, regional positivity with desmin and myogenin, but negative for MyoD1. Limited fusion analysis by RT-PCR was negative for fusions involving *PAX3/PAX7-FOXO1*, *EWSR1*, *SS18-SSX1/SSX2*, and *ETV6-NTRK3* leading to a provisional diagnosis of infantile rhabdomyofibrosarcoma. As wide local excision or radiation would be excessively morbid, the decision was made for the patient to complete 16 cycles of VAC followed by 4 cycles of VA. Surveillance MRIs have shown no new evidence of disease, currently 5 years off therapy.

Patient 2 was a term baby born via emergent C-section for fetal distress and intubated for poor APGARs and hypoxic ischemic event. A large abdominal mass arising from the right kidney was noted on imaging with intra-abdominal hemorrhage, and associated with hypertension and coagulopathy requiring factor and product replacement. On day of life 2, an exploratory laparotomy with resection of a ruptured right renal tumor was performed. Pathology demonstrated a spindle cell tumor negative for fusions involving *EWSR1*, *SS18-SSX1/SSX2*, and *ETV6-NTRK3* by RT-PCR. The patient was given a provisional diagnosis of congenital mesoblastic nephroma (CMN)/IFS. Staging and surveillance imaging demonstrated no evidence of disease. The patient was observed and has no radiographic evidence of disease at 16 months of age.

Patient 3 was diagnosed at 6 months of age with a right renal mass following a one week history of increasing abdominal distension. Gross total resection with lymph node sampling was completed and revealed an undifferentiated sarcomatous lesion with histologic features suggestive of a cellular CMN invading the renal sinus and renal capsule. Tumor cells were focally present at the cauterized margin. Immunohistochemical stains were positive for vimentin, WT-1, pan-cytokeratin (patchy), SMA (focal), cyclin-D1 (patchy), and p53. The tumor was negative for *ETV6-NTRK3* fusion transcript by RT-PCR.

Genomic profiling was performed from tumors obtained from all three patients. A recurrent internal tandem duplication (ITD) including exons 18-25 of *EGFR* (NM_005228) was identified in all three patients. This intragenic rearrangement results in duplication of the kinase domain and a constitutively active protein. This finding revised the diagnosis for all three patients: Patient 1 revised to infantile fibrosarcoma (IFS) with *EGFR*-ITD; Patient 2 revised to CMN with *EGFR*-ITD; Patient 3 revised to stage III CMN with *EGFR*-ITD.

Conclusion: The detection of *EGFR* driver mutations is non-standard in the workup of infantile tumors but increasing evidence indicates that they are more common than previously known. Advances in molecular profiling are expanding our ability to detect these events. In a recent case series of seven *ETV6-NTRK3* fusion-negative CMNs, five of the tumors harbored *EGFR*-ITD and a sixth had a splice-site mutation. In another series, *EGFR*-ITD was found in 10 of 10 classical CMNs and overall 43 of 80 CMNs, but no other childhood renal tumors, establishing it as a distinguishing marker for classical CMN. Our cases highlight the utility of broader molecular profiling, complementary methods for detection of a spectrum of disease-associate variants, and support the emerging importance of *EGFR* mutations in CMN and IFS.

Poster #130 3462585

GENOMIC CHARACTERISTICS RELATED TO THE EFFICACY OF ANLOTINIB IN LEIOMYOSARCOMA

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Objective: Leiomyosarcoma (LMS) is one of most common sarcoma subtypes. Treatment options of LMS are limited. Anlotinib, an angiogenesis inhibitor targeting to multiple tyrosine kinases, was recently approved by China FDA for the second line treatment of advanced LMS. Although the disease control rate (DCR) was about 60% higher than the placebo, the selection of LMS pts who are suitable for the treatment of Anlotinib is still a challenge. We thus performed whole exome sequencing (WES) and transcriptome analysis on LMS samples with the hope to identify the genetic factors that can predict the efficacy of Anlotinib.

Methods: The study includes 18 pretreated, advanced LMS pts who received Anlotinib 12mg qd po for 2 weeks followed by a rest of one week. The clinical response was evaluated by RECIST 1.1. WES was conducted on blood/tumor pairs for all patients (2 PR, 10 SD and 6 PD) and RNA-seq was further conducted on 12 cases (8 SD and 4 PD). We then did WES and differential analysis of transcriptome to search for genetic factors that are corelated with the efficacy of anlotinib.

Results: TP53 is the tumor-related gene with highest mutation rate, but the mutation ratio was the same between SD+PR group (50%) and PD group (50%)（Fig. 1A）. It's worth noting that PAK2 was the most significant somatic mutant gene between SD+PR and PD group (17% vs 100%, p=0.0015) (Fig. 1B). As for SCNA, the amplification of FZR1（0% vs 67%, p=0.0049）and JUN (17% vs 83%, p=0.0128) mainly occurred in PD group (Fig. 1C&D). COSMIC mutational signature 6 and 15, related to DNA mismatch repair, were enriched in SD+PR group (Fig. 2). In the view of transcriptome, 333 genes were upregulated in SD, 96 genes were upregulated in PD group (Foldchange ≥2) (Fig. 3). The genes upregulated in SD group were mainly enriched in immune system response pathway and inflammatory response pathway (Fig. 3B). While the genes upregulated in PD group were largely involved in RNA metabolic process and dicarboxylic acid catabolic process (Fig. 3C).

Conclusion: Activation of DNA mismatch repair, immune system response, and inflammatory response pathways predict better prognosis in the treatment of Anlotinib. PAK2 mutation and the SCNV of FZR1 and JUN were correlated with the worse efficacy of Anlotinib in LMS. And the metabolic of RNA and dicarboxylic acid may interfere with the response of Anlotinib.

Fig1 Somatic mutations and CNV between SD+PR group and PD group.

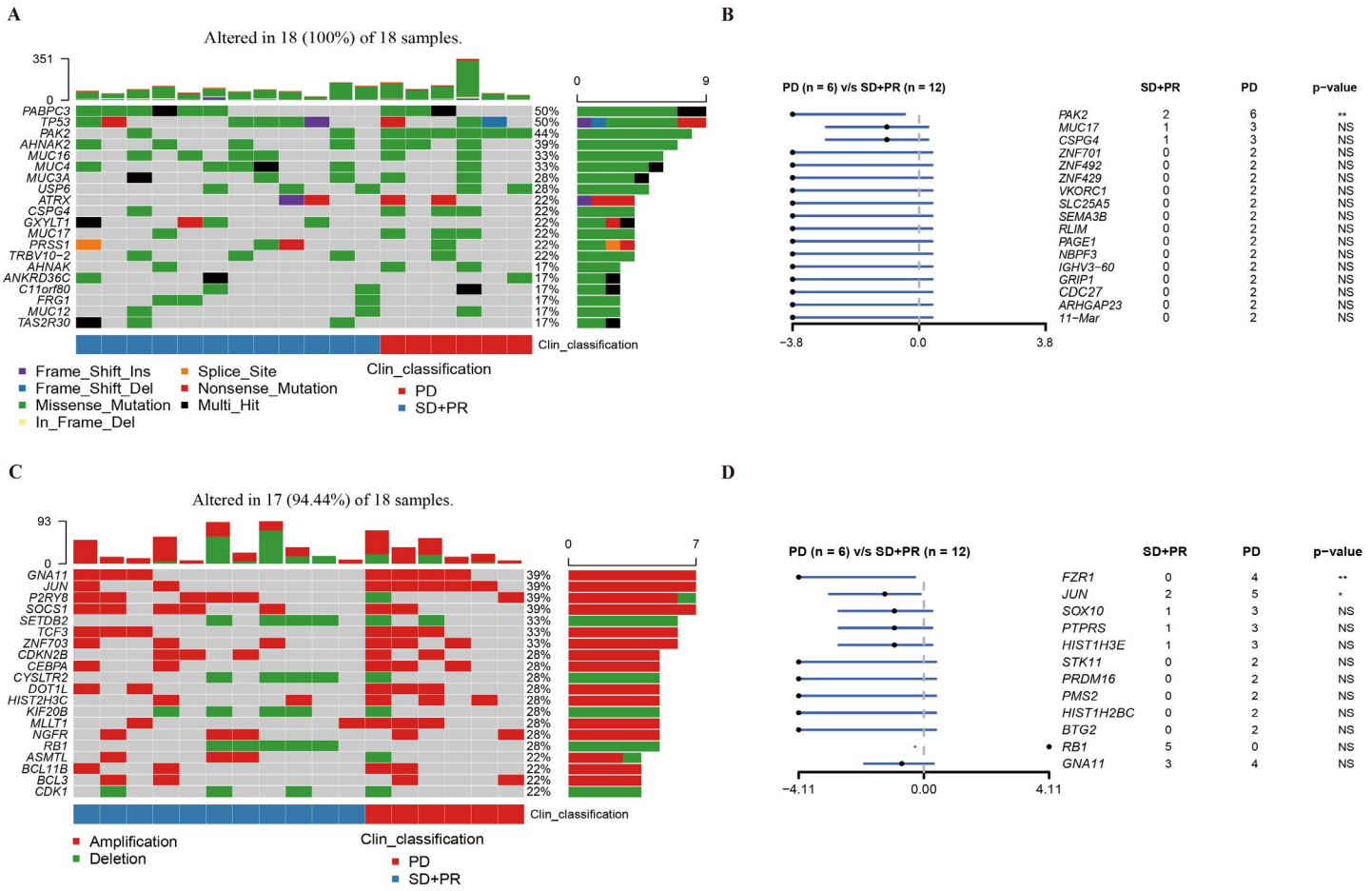

Figure 1 Somatic mutations and copy number variations between SD+PR group and PD group. (A) TOP 20 genes with highest variation in frequency of somatic SNVs and indels between SD+PR group and PD group. (B) Significantly differential mutation genes were analyzed between SD+PR group and PD group. (Fisher's exact test, $p<0.05$). (C) TOP 20 CNVs with highest frequency between SD+PR group and PD group. (D) Significantly differential CNVs were analyzed between SD+PR group and PD group. (Fisher's exact test, $p<0.05$)

Figure 2 Mutational signatures in SD+PR group and PD group.

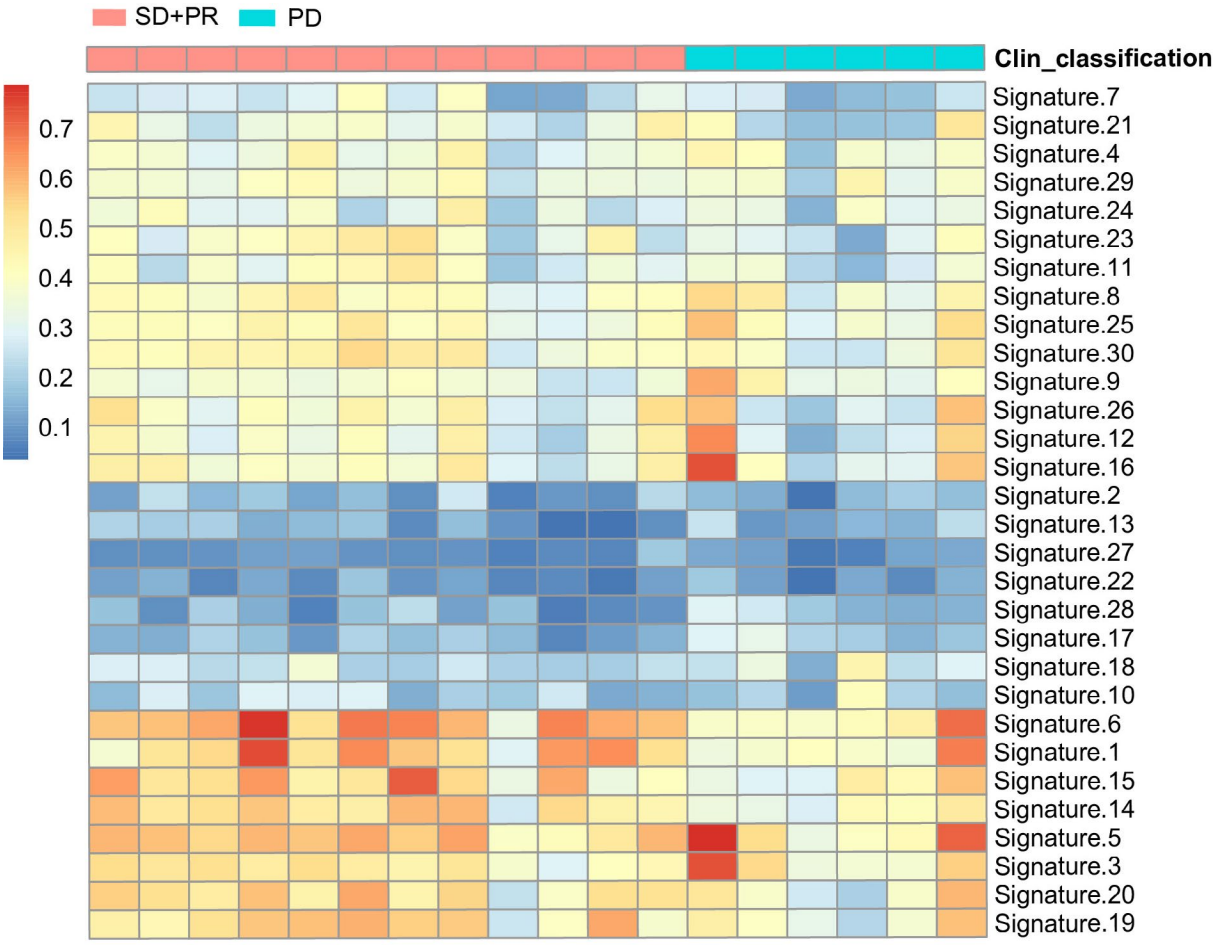

Figure 3 Differential expressed genes in SD and PD group.

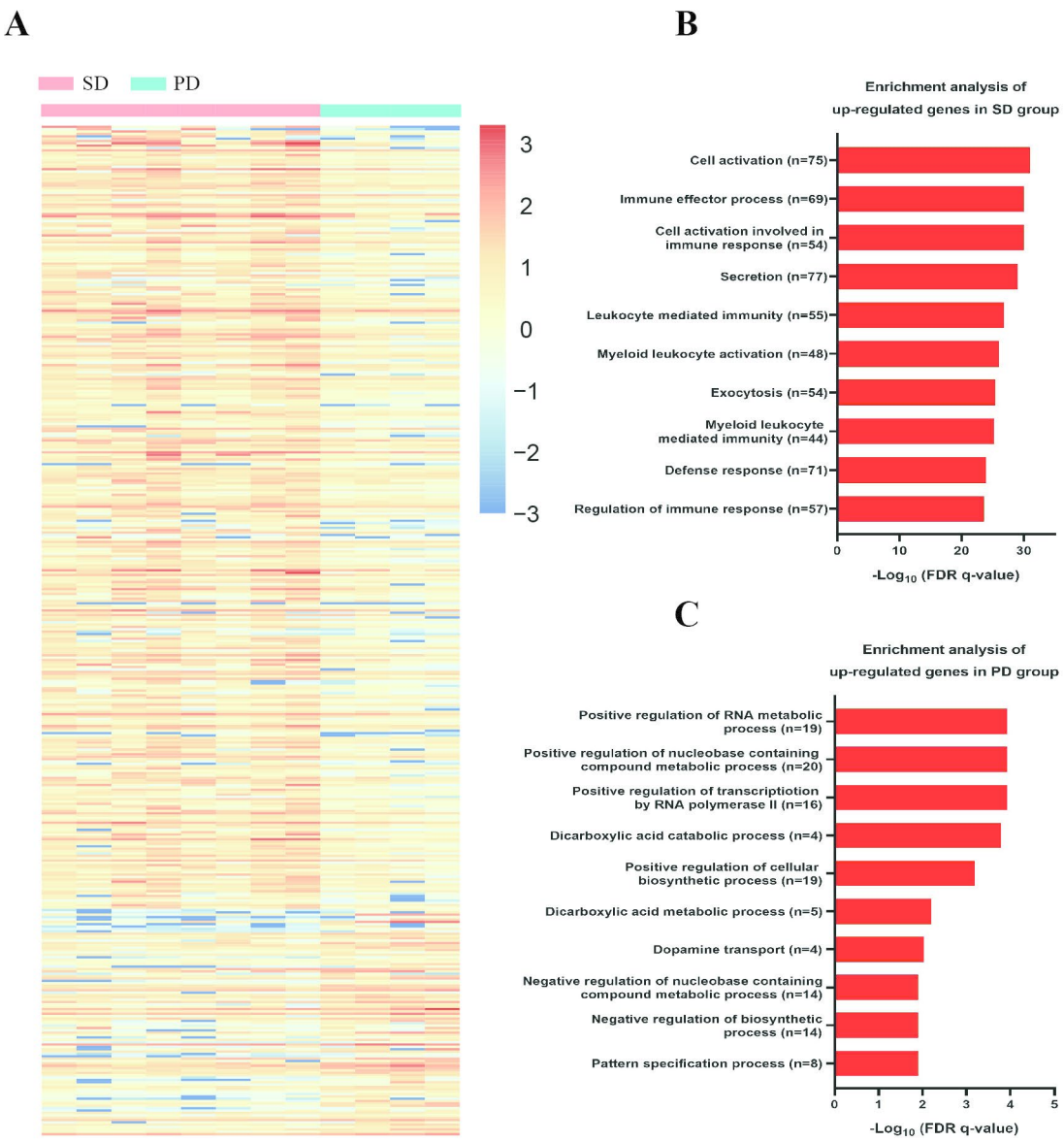

Figure 3 Differential expressed genes in SD and PD group. (A) Heatmap of significantly differential expressed genes in SD group and PD group. (B) TOP 10 enriched pathways of significantly differential expressed genes in SD group. (C) TOP 10 enriched pathways of significantly differential expressed genes in PD group.

Poster #131 3462616

DESPITE ADVANCES IN TUMOR MANAGEMENT MODALITIES, SURGERY SEEMS TO BE THE BEST PREDICTOR OF SURVIVAL FOR OSTEOSARCOMA: AN ANALYSIS OF PRIMARY OSSEOUS TUMOR CHARACTERISTICS, MANAGEMENT, AND OUTCOMES FROM THE NATIONAL CANCER DATABASE (NCDB)

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Objective: Primary osseous tumors, such as osteosarcoma, are relatively uncommon. Most studies about their characteristics, management, and outcomes have limited patient numbers and combine varied tumor histology. Further, the management of such neoplasms has evolved significantly within the past decade, as surgical techniques, adjuvant therapies, and molecular-targeted treatment modalities. and as such, most studies are from a single-institution with varying tumor histology making them difficult to study. Further, the management of such neoplasms has evolved significantly within the past decade, as surgical techniques, percutaneous techniques, radiation therapy (RT), and molecular sequencing have developed as viable treatment options. With respect to RT, despite delivery becoming increasingly tumor-specific, with high-tech photon-based intensity-modulated RT, high-dose single-fraction radiosurgery, proton beam RT, and carbon ion beam as potential options, these options remain expensive and with variable outcomes. Furthermore, tumor-specific therapies have emerged such as receptor of activator nuclear factor kappa-B ligand (RANKL) inhibitors and percutaneous thermal ablation which have shown static outcomes.

Given osteosarcoma treatment advances, the current study sought to investigate the effect of various treatment modalities and demographic risk factors on the outcomes of primary osteosarcoma using the large National Cancer Database (NCDB).

Methods: Osteosarcoma patients from the 2004-2015 NCDB datasets were separated into three cohorts based on primary tumor location: axial, appendicular, and other. Demographic and treatment data as well as one-, five-, and 10-year survival were determined for each group. Multivariate Cox analysis was performed showing the correlation of demographic and treatment variables with the likelihood of death at any given time within each group. Kaplan Meier survival curves were generated showing the correlation of survival with distant metastases and year of diagnosis.

Results: Of 4,430 osteosarcoma patients identified, 810 cases were axial and 3,435 were appendicular. Multivariate Cox analysis showed that the likelihood of death for all patients significantly increased with age category, distant metastases (Incidence Rate Ratio (IRR = 3.83, $p \leq 0.001$), and treatment with radiation alone (IRR = 7.35, $p < 0.001$) and significantly decreased for appendicular primary site (IRR = 0.71, $p < 0.001$), and treatment with surgery alone (IRR = 0.38, $p < 0.001$) or surgery plus chemotherapy (IRR = 0.60, $p < 0.001$).

Analysis of axial and appendicular tumors separately, the likelihood of death for the axial group significantly increased with age, distant metastases (IRR = 3.39, $p < 0.001$), and treatment with chemotherapy (IRR = 1.68, $p = 0.001$), but decreased with surgical treatment (IRR = 0.44, $p < 0.001$). Additionally, the likelihood of death for the appendicular group increased significantly with age, metastases (IRR = 3.96 $p < 0.001$), and radiation treatment (IRR = 16.575, $p = 0.006$), and decreased significantly for females (IRR = 0.80, $p < 0.001$), surgical treatment (IRR = 0.30, $p < 0.001$), and treatment with surgery plus chemotherapy (IRR = 0.48, $p < 0.001$).

Conclusion: Despite advances in tumor management, the current study found surgical excision to be the best predictor of survival for both axial and appendicular osteosarcomas. There is no difference in patient survival from 2004 to 2015 suggesting that newer therapies may be equally effective compared to traditional management of osteosarcoma. Presence of distant metastases is a significant, poor prognostic sign as is increasing age and male gender. Presence of primary osteosarcoma of the appendicular skeleton was found to be a good prognostic sign when compared to axial involvement potentially due to ease of operability.

Figure 1A: Long-term survival of patients in the axial, appendicular, and other cohorts ($p < 0.001$).

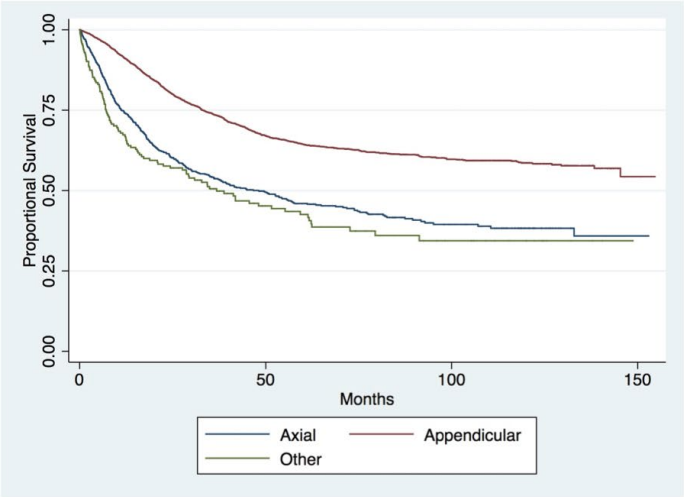


Figure 1B: Long-term survival of patients in the three different era groups ($p = 0.022$).

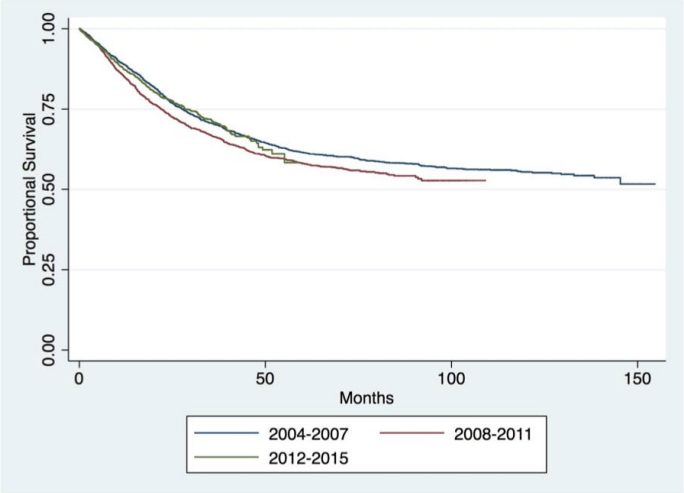
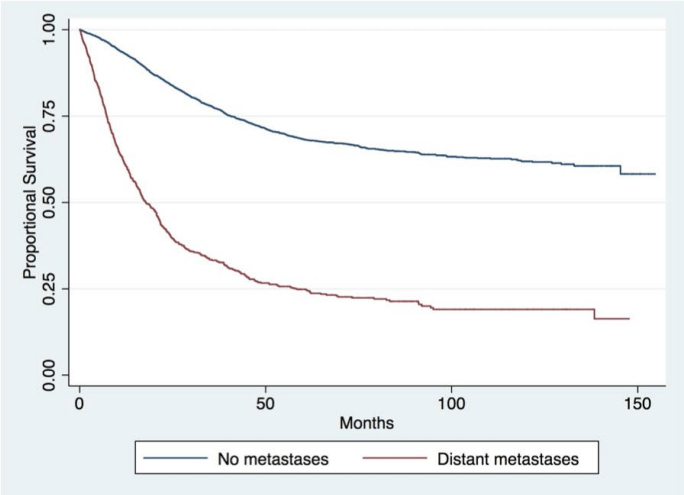


Figure 1C: Long-term survival of all patients with and without distant metastases at the time of presentation ($p < 0.001$).



Three different Kaplan Meier curves showing likelihood of survival based on site, year of procedure, and presence of metastasis at the time of diagnosis.

Table 1: Multivariate Cox analysis of the likelihood of death at any given time for demographic and operative variables across all patients.

Demographic Factors	IRR	95% CI		95% CI	p-value
Age Category					
< 23	Ref	Ref		Ref	Ref
23-45	**1.325**	**1.162**	**-**	**1.51**	**< 0.001**
46-62	**2.116**	**1.815**	**-**	**2.467**	**< 0.001**
62+	**3.743**	**3.061**	**-**	**4.578**	**< 0.001**
Sex					
Male	Ref	Ref		Ref	Ref
Female	**0.800**	**0.725**		**0.883**	**<0.001**
Race					
White	Ref	Ref		Ref	Ref
Black	1.177	1.025	-	1.351	0.021
Hispanic	0.947	0.807	-	1.11	0.5
American Indian/Eskimo	1.144	0.67	-	1.952	0.623
Asian	1.244	0.956	-	1.618	0.104
Other	0.933	0.75	-	1.161	0.536
Charles Deyo Score	1.135	1.004	-	1.282	0.042
Site					
Axial	Ref	Ref		Ref	Ref
Appendicular	**0.707**	**0.624**	**-**	**0.802**	**<0.001**
Other	0.858	0.690	-	1.067	0.169
Metastasis at time of diagnosis					
Yes	**3.833**	**3.437**	**-**	**4.274**	**<0.001**
Year of diagnosis					
2004-2007	Ref	Ref		Ref	Ref
2008-2011	1.101	0.986	-	1.228	0.086
2012-2015	0.953	0.831	-	1.093	0.492
Insurance Status			-		
Private Insurance	Ref	Ref		Ref	Ref
Not insured	1.205	0.973	-	1.493	0.087
Medicaid	1.025	0.896	-	1.172	0.719
Medicare	1.283	1.059	-	1.556	0.011
Other government	0.794	0.544	-	1.16	0.233
Unknown	0.781	0.604	-	1.009	0.058
Treatment choice					
None	Ref	Ref		Ref	Ref
Surgery	**0.380**	**0.306**	**-**	**0.472**	**<0.001**
Radiation	**7.347**	**2.673**	**-**	**20.196**	**<0.001**
Chemotherapy	1.224	1.020	-	1.470	0.03
Surgery and radiation	0.734	0.520	-	1.037	0.079
Surgery and chemotherapy	**0.597**	**0.503**	**-**	**0.708**	**<0.001**
Radiation and chemotherapy	5.929	1.451	-	24.233	0.013
Unknown	**0.541**	**0.384**	**-**	**0.763**	**<0.001**

Multivariate cox analysis of the likelihood of death at any given time for demographic and operative variables across all patients

Poster #132 3462658

THE EFFECT OF EXTENSOR MECHANISM REPAIR ON FUNCTIONAL OUTCOME FOLLOWING PROXIMAL TIBIA REPLACEMENT

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Objective: Proximal tibial replacements (PTRs) are becoming an increasingly common surgical option for patients following bone tumor resection. However, there is debate regarding the optimal method of extensor mechanism repair. This study analyzed modes of failure for PTRs as well as postoperative outcomes based on method of extensor mechanism repair.

Methods: 93 PTRs performed at a single institution by one of two surgeons were retrospectively reviewed. Demographic, failure, extensor mechanism repair and functional outcome data were analyzed. Extensor mechanism repair was performed either by attaching the patella tendon directly to the prosthesis or by reattaching the patella tendon to a transposed medial gastrocnemius flap. Statistical significance was defined as $p < 0.05$ using a Student's t-test.

Results: 93 PTRs performed on 70 patients were included. Average age at time of first surgery was 26.2 years (range: 10.7–86.7) and average follow-up time was 10.0 years (range: 0.02–34.1). 37 PTRs (39.8%) failed at an average time of 6.8 years after surgery. 10 out of 12 failures due to aseptic loosening occurred greater than 2 years after the time of surgery. 5 out of 6 failures due to infection occurred greater than 2 years after the time of surgery. 8 other PTRs failed structurally failed, 7 failed due to tumor progression and 4 failed due to soft tissue failure. Patella tendon reattachment directly to the prosthesis resulted in a significantly higher rate of extensor lag at the most recent follow-up (68.4%) as compared patella tendon reattachment to a medial gastrocnemius flap (35.7%, $p = 0.043$).

Conclusion: This study determined that PTR failures due to either aseptic loosening or infection tended to occur late. This study also emphasized that careful consideration regarding the method of extensor mechanism repair should be taken on a case by case basis prior to undergoing PTR.

Table 1: Proximal Tibia Replacement Failures

Mode of Failure	Time to Failure (Years) (Mean/Median)	Percent of Failures
Soft tissue Failure	7.2/7.5	10.8% (4/37)
Aseptic Loosening	15.8/16.6	32.4% (12/37)
Structural Failure	6.1/4.5	21.6% (8/37)
Infection	10.1/11.8	16.2% (6/37)
Tumor Progression	1.8/0.7	18.9% (7/37)
Total	6.79/5.29	39.8% of all implants (37/93)

Failure modalities based on the Henderson Failure Classification

Table 2: Functional Outcome After Extensor Mechanism Reconstruction

	Patella tendon directly to prosthesis (n = 20)	Patella tendon to gastrocnemius flap (n = 48)	P-value
Age (Years) (Mean/Median)	30.9/26.9	29.3/22.1	0.747
Gender (Male/Female)	60%/40%	54.2%/45.8%	0.567
F/u time (Years) (Mean/Median)	10.2/7.0	8.3/8.2	0.33
Extensor lag at 1 year? (Y/N)	12/7	11/19	0.032
Degrees of extensor lag at 1 year (Mean/Median)	15.8/7.5	11.7/0	0.44
Extensor lag at most recent follow-up? (Y/N)	13/6	15/27	0.043
Degrees of extensor lag at most recent follow-up (Mean/Median)	17.1/10	7.9/0	0.031

Poster #133 3462660

SURVIVAL FOLLOWING EPITHELIOID SARCOMA DIAGNOSIS: A SEER DATABASE ANALYSIS

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Objective: Epithelioid sarcoma (ES) is an ultra-rare, poor prognosis, soft tissue sarcoma frequently associated with a SMARCB1 gene mutation. Little data exist beyond single-institution, case series to inform clinical practice and trial design. The objective of this study was to determine predictors of survival and inform future clinical trial design.

Methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified 885 patients diagnosed with ES between 1975-2016. Descriptive statistics defined demographic and clinical characteristics. Kaplan-Meier survival analysis was used to determine overall survival (OS) at 3, 6, 12, 24, and 36 months (mos) by SEER summary stage (local, regional, distant) and subtype (categorized as proximal versus distal based on primary location). Cox regression was used to identify factors associated with OS. We assessed the interaction between surgery and stage, controlling for all variables significant in univariable analysis.

Results: Mean age at diagnosis was 45 years (median [me] 44, range [R] 0-97). Fifty-five percent (n=489) were male and 81% were white (n=719; n=106 [12%] Black; n=60 [7%] other race). Tumors were on average 6.5 cm (me=5.2, R 0-35), SEER grade III/IV 41%, local stage 51%, and proximal type/location 51% (n=453). Median OS for local, regional and distant stages were 234 (95% confidence interval [95%CI]177-326 mos), 37 (25-59 mos 95%CI) and 5 (4-7 mos 95%CI) months, respectively. Median OS for distal ES was 177 mos (108-248 mos CI) versus 22 mos (16-33 mos CI) for proximal subtype (see Table 1). In multivariable Cox analysis, sex and receipt of either radiation or chemotherapy were not associated with OS. In contrast, age>44 years, Black race, size>5 cm (or missing), proximal subtype and increasing stage were all significantly associated with inferior OS. Lower grade, later year of diagnosis and receipt of surgery were associated with superior OS. In addition, the interaction of surgery and stage was statistically significant, demonstrating that receipt of surgery was beneficial across all stages, including for those with metastatic disease, after controlling for all significant variables (see Table 2 and Figure 1).

Conclusion: Survival from ES remains poor, particularly for patients with advanced stage, proximal subtype, or unresectable disease. Future trial designs should account for these factors in addition to age. Given that surgery is associated with improved survival regardless of stage at diagnosis, future clinical trials and regulatory authorities should consider the attainment of complete surgical resection in previously unresectable ES cases as a meaningful, positive primary outcome.

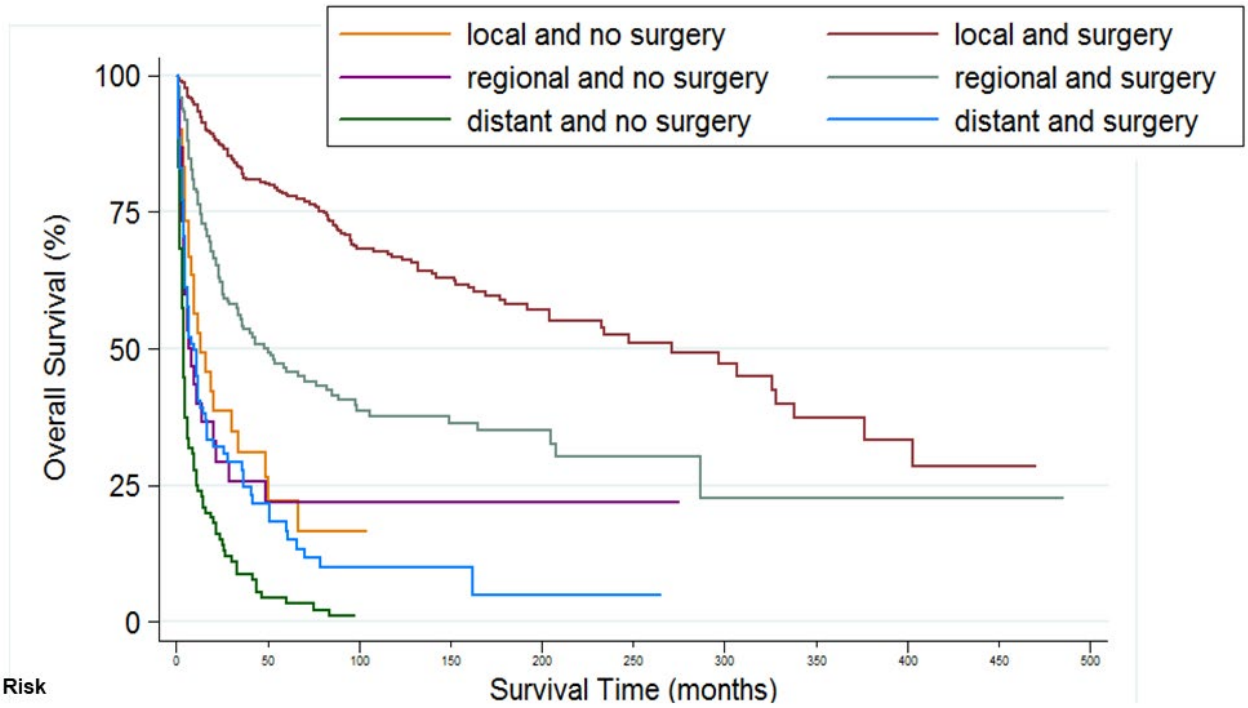
Table 1: Overall survival in months (with 95% confidence interval [CI]) by stage and subtype/location for common clinical trial milestones.

	3 months (95% CI)	6 months (95% CI)	12 months (95% CI)	24 months (95% CI)	36 months (95% CI)	Median (95% CI)
Local n=454	98% (96%-99%)	95% (92%-96%)	91% (88%-93%)	84% (80%-87)	79% (74%-82%)	234m (177m-326m)
Regional n=229	91% (87%-94%)	83% (78%-88%)	71% (65%-77%)	57% (51%-64%)	50% (43%-57%)	37m (25m-59m)
Distant n=202	66% (59%-72%)	44% (37%-51%)	31% (25%-38%)	22% (17%-29%)	17% (12%-23%)	5m (4m-7m)
Distal n=432	96% (93%-97%)	92% (88%-84%)	86% (83%-89%)	79% (75%-83%)	72% (67%-76%)	177m (108m-248m)
Proximal n=453	82% (79%-86%)	69% (65%-74%)	59% (54%-63%)	48% (43%-53%)	43% (38%-48%)	22m (16m-33m)
No Surgery for Local Stage, n=30	87% (68%-95%)	73% (54%-86%)	53% (34%-69%)	39% (21%-56%)	31% (15%-48%)	13m (7m -34m)
Surgery for Local Stage, n=424	99% (97%-100%)	96% (94%-98%)	93% (91%-95%)	87% (84%-90%)	82% (78%-86%)	271m (204m-338m)
No Surgery for Regional Stage, n=30	73% (54%-86%)	53% (34%-69%)	40% (23%-57%)	29% (14%-46%)	26% (12%-42%)	7m (4m-20m)
Surgery for Regional Stage, n=199	94% (90%-97%)	88% (83%-92%)	76% (70%-82%)	62% (55%-69%)	54% (46%-61%)	50m (33m-82m)
No Surgery for Distant Stage, n=114	57% (48%-66%)	34% (25%-42%)	24% (16%-32%)	15% (9%-23%)	9% (4%-15%)	4m (3m-5m)
Surgery for Distant Stage, n=88	77% (67%-85%)	58% (47%-67%)	40% (30%-50%)	32% (23%-42%)	28% (19%-38%)	10m (6m-13m)

Table 2: Hazard ratios with 95% confidence intervals [CI] and p-values from for comparisons by stage and receipt of surgery, controlling for significant confounding variables (Cox regression model).

	Hazard ratio (95% confidence interval), p-value
Referent: Surgery for Local Stage (n=424)	--
No Surgery for Local Stage (n=30)	3.35 (2.11-5.33), <0.001
Referent: Surgery for Regional Stage (n=199)	--
No Surgery for Regional Stage (n=30)	1.60 (1.00-2.55), 0.048
Referent: Surgery for Distant Stage (n=114)	--
Surgery for Distant Stage (n=88)	1.89 (1.37-2.61), <0.001
Referent: Surgery for Local Stage (n=424)	--
Surgery for Regional Stage (n=199)	2.12 (1.63-2.75), <0.001
Surgery for Distant Stage (n=88)	5.64 (4.19-7.59), <0.001
Referent: Surgery for Local Stage (n=424)	--
No Surgery for Regional Stage (n=30)	3.39 (2.12-5.14), <0.001
No Surgery for Distant Stage (n=114)	10.68 (7.92-14.41), <0.001

Figure 1: Overall survival in months by stage at presentation and receipt of surgery (Kaplan-Meier survival analysis).



Number at Risk

Local and no surgery	30	1	0	0	0	0
Local and surgery	424	161	62	4	7	0
Regional and no surgery	30	4	1	0	0	0
Regional and surgery	199	39	15	3	1	0
Distant and no surgery	114	0	0	0	0	0
Distant and surgery	88	6	1	0	0	0

Poster #134 3462671

THE INCIDENCE, RISK FACTORS AND MICROBIAL PROFILE OF INFECTED ENDOPROSTHETIC RECONSTRUCTRIONS

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Objective: Periprosthetic infection is one of the most feared complication following endoprosthetic reconstruction and results in revision surgeries, amputation or even death. Understanding the risk factors for and microbial profile of these infections is crucial to the development of effective prevention and treatment strategies. The objective of this study was to utilize a large database of endoprostheses to describe the incidence of and risk factors for infection and to characterize the microbial profile of such infections in order to help guide management.

Methods: A retrospective review of 813 endoprosthetic reconstructions from January 1, 1980 to December 31, 2019 at a single institution was performed. Demographic, oncologic, procedural and outcome data was collected and analyzed. The primary outcome of interest was infection resulting in revision surgery or amputation. Prostheses that became infection were compared with uninfected prostheses in order to identify risk factors. Cultured organism(s) were analyzed and stratified by anatomic location.

Results: 54 out of 813 (6.6%) endoprosthetic reconstructions resulted in infection. The incidence of infection was higher for revision implants (25/187, 13.4%) compared with primary implants (29/626, 4.6%). Age at the time of surgery was significantly higher in the infected group (42.9 +/- 19.6 years) versus the uninfected group (36.1 +/- 21.2 years, p = .014). No significant association was found between infection and perioperative chemotherapy (p = 0.39) or perioperative radiation therapy (p = 0.63). Culture data was unavailable for 6 infected endoprosthesis. *S. aureus* and *S. epidermidis* were the most commonly cultured organisms with an incidence of 35.5% (17/48) and 20.8% (10/48), respectively. 22.9% (11/48) of cultures were polymicrobial and 8.3% (4/48) of cultures did not grow any organisms. 47.0% (8/17) of *S. aureus* infections were methicillin-resistant and 42.9% (3/7) of *Enterococcal* infections were vancomycin-resistant.

Conclusion: Comprehensive knowledge of the risk factors for and the microbial profile of endoprosthetic infections is crucial to developing effective prevention and treatment strategies. This study demonstrates a relatively high incidence of polymicrobial and antibiotic-resistant infections. Continually maintaining an awareness of these rates is paramount when determining effective antibiotic regimens.

Table 1: Risk Factors for Polymicrobial Infection

	MONOMICROBIAL INFECTIONS (n = 37)	POLYMICROBIAL INFECTIONS (n = 11)	P-VALUE
Age at time of surgery years (Mean/Median)	40.9 (40.1)	52.5 (57.9)	0.028
Gender (M:F)	18:19	6:5	0.483
Percent of Patients with Wound Complications (n)	18.9% (7)	81.8% (9)	< 0.0001
Percent of Patients Receiving Chemotherapy (n)	27.0% (10)	36.4% (4)	0.89
Percent of Patients Receiving Radiation Therapy (n)	5.4% (2)	27.3% (3)	0.158

Data unavailable for 6 infected endoprostheses

Figure 1

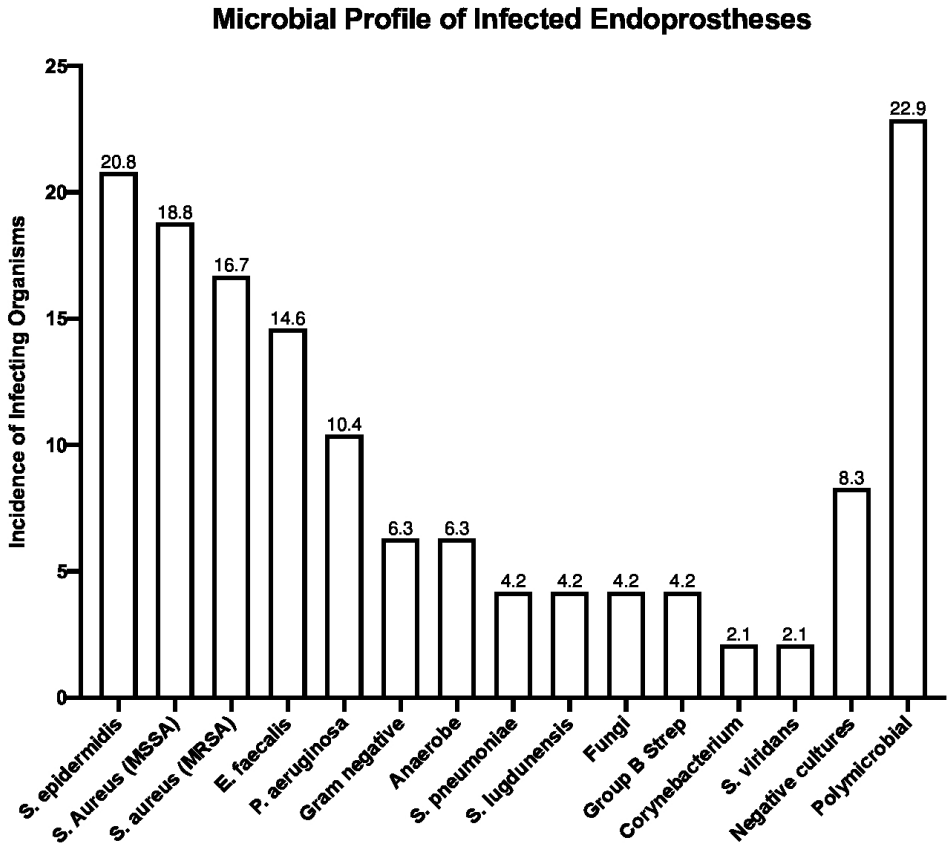

Figure 1: Microbial profile of infected endoprostheses showing that most infections were polymicrobial in nature. *S. aureus*, *S. epidermidis* and *E. faecalis* were the most common monomicrobial infections. Culture data for 6 infected endoprosthetic reconstructions were not available. Gram negative organisms included *Enterobacter cloacae, Citrobacter koseri* and *Stenotrophomonas maltophilia*. Anaerobic organisms included *Propionibacterium acnes, Actinomyces neuii* and *Finegoldia magna*. Fungi included *Candida albicans* and *Rhodotorula mucilaginosa*.

Poster #135 3462922

SURGICAL TREATMENT PATTERNS AND HEALTHCARE RESOURCE UTILIZATION IN PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMORS WHO UNDERWENT JOINT SURGERY IN THE UNITED STATES

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Objective: Tenosynovial giant cell tumors (TGCT) are synovial aggressive neoplasms, causing pain, joint dysfunction and damage to affected joint. Surgery is often curative when tumors can be completely removed. Little is known about the patterns of surgery and healthcare resource utilization (HRU). This study describes surgical pattern and HRU in patients with TGCT who underwent joint surgery.

Methods: Patients newly diagnosed with TGCT aged 18-64 years who underwent joint surgery post-TGCT diagnosis were identified in the OptumHealth Care Solutions, Inc. US claims database (Q1 1999 - Q1 2017). The index date was defined as the date of the first TGCT diagnosis; all patients were required to be continuously enrolled for ≥1 year before and ≥3 years after the index date. First and repeat joint surgeries (arthroplasty, arthrodesis, arthroscopic excision, open excision, and amputation) were described from the index date until the end of data availability. Concomitant medications, medical visits and procedures in year 1, year 2 and year 3 post-index were compared with those in the year pre-index (baseline).

Results: The study identified 462 TGCT patients (67% males; mean age: 46 years) who underwent joint surgery. *Surgical patterns:* During the median follow-up of 5.7 (range: 3-15.2) years post-index, 78% of patients received first joint surgery in year 1, 6% in year 2, 5% in year 3, and 11% in subsequent years. The median time from the index diagnosis to the first joint surgery was 25 days, although 103 patients did not have surgery until the second year or later. During the study period, a total of 187 patients had at least one repeat surgery; the mean (standard deviation) number of repeat surgeries for them was 1.73 (1.18). Among the 359 patients who had their first surgery in year 1, 43% had repeat surgeries (13% in year 1, 8% in year 2, 7% in year 3, and 15% after year 3).

HRU: MRI was performed in 46% patients at baseline, and its utilization was significantly reduced post-index. Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) were commonly used at baseline. The use of opioid and NSAIDs increased significantly in year 1 ($p<0.001$) and returned to similar or lower level than baseline in year 2 and later. The use of systemic corticosteroids remained stable at 18-19% in three years post-index. While a small number of patients used DMARDs, a significant increase in their use was observed in year 3. Except for ER visits, rates of inpatient admissions and outpatient visits surged in year 1 and returned to baseline level or lower later. Surgeons were the most commonly visited specialists in outpatient visits (86% at baseline and 89% in year 1). More patients used physical/occupational/rehabilitation services in year 1; utilization of these services returned to baseline level in subsequent years.

Conclusion: Although surgical resection is the first line treatment for TGCT, not all patients received surgical resection immediately after diagnosis, in some cases (11%) having the first surgery more than three years post diagnosis. Many patients underwent one or more repeat operations, suggesting surgical resection alone may be inadequate to control TGCT for these patients. HRU was highest in the first year post diagnosis when most surgeries were observed. Decreased utilization of MRI in the years following surgery suggests MRI was not commonly used to detect recurrence. Utilization of opioids and NSAIDs, physical/occupational/rehabilitation services, and outpatient visits with surgeons remained prevalent more than 2 years after TGCT diagnosis. These data highlight challenges for both surgeons and the healthcare system in the diagnosis and treatment of TGCT, and the need for effective treatment options to reduce the burden for the TGCT patients after surgical treatment.

	Patients with TGCT undergoing joint surgery in the 3 years post-index N = 462			
	Baseline	**Year 1**	**Year 2**	**Year 3**
Patients undergoing any joint surgery, N (%)	38 (8)	359 (78)	63 (14)	71 (15)
First joint surgery post index[1]	-	359 (78)	29 (6)	23 (5)
First repeat joint surgery post index[2]:				
Patients with first surgery in year 1 (N = 359)	-	45/359 (13)	27/359 (8)	25/359 (7)
Patients with first surgery in year 2 (N = 29)	-	-	3/29 (10)	6/29 (21)
Patients with first surgery in year 3 (N = 23)	-	-	-	1/23 (4)
Patients with prescriptions for selected medications, N (%)				
Opioid	209 (45)	359 (78)*	187 (41)	196 (42)
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	184 (40)	226 (49)*	164 (36)	149 (32)*
Systemic corticosteroids	83 (18)	86 (19)	82 (18)	88 (19)
Disease modifying anti-rheumatic agents (DMARDs)	15 (3.2)	20 (4.3)	22 (4.8)	25 (5.4)*
Patients with Magnetic Resonance Imaging (MRI), N (%)	210 (46)	128 (28)*	78 (17)*	87 (19)*
Patients with healthcare visits				
Inpatient admissions[3], N (%)	55 (12)	113 (25)*	43 (9)	44 (10)
Number of inpatient admissions per patient, mean ± SD	0.4 ± 1.9	0.7 ±1.9*	0.4 ± 2.0	0.4 ± 3.2
ER visits, N (%)	111 (24)	130 (28)	94 (20)	103 (22)
Number of emergency room visits/patient, mean ± SD	0.4 ± 0.9	0.6 ± 2.0*	0.4 ± 1.5	0.4 ± 1.5
Outpatient visits, N (%)	452 (98)	461 (100)*	434 (94)*	443 (96)
Number of outpatient visits/patient, mean ± SD	16.5 ± 18.4	24.2 ± 20.3*	15.3 ± 17.8*	14.9 ± 15.4*
Patients with specific specialist/medical management outpatient visits, N (%)				
Surgeon	396 (86)	410 (89)*	238 (52)*	217 (47)*
Non-surgical orthopedist	62 (13)	65 (14)	50 (11)	47 (10)
Rheumatologist	20 (4)	31 (7)*	22 (5)	17 (4)
Oncologist	4 (1)	5 (1)	4 (1)	10 (2)
Physical/occupational/rehabilitation	138 (30)	268 (58)*	132 (29)	137 (30)
Chiropractic	66 (14)	58 (13)	61 (13)	71 (15)
Acupuncture	3 (1)	7 (2)	8 (2)	9 (2)
Osteopathic	9 (2)	8 (2)	8 (2)	7 (2)

* Statistically significant compared to baseline value (i.e., $p < 0.05$ using McNemar's tests for proportions and Wilcoxon signed rank-sum tests for counts)

1. Among 462 patients who underwent surgery post index, 51 (11%) patients underwent the first surgery after year 3.
2. Repeat surgery was defined as the joint surgery received more than 30 days after the previous surgery. Among 462 patients, 80 (17%) patients underwent the first repeat surgery after year 3.
3. Inpatient admissions did not include same day surgeries, which were classified as outpatient visits.

Poster #136 3462983

GEMCITABINE-CONTAINING REGIMENS FOR THE TREATMENT OF METASTATIC MYXOFIBROSARCOMA REFRACTORY TO DOXORUBICIN

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Objective: Myxofibrosarcoma is a frequent type of soft-tissue sarcoma, and is associated with high rates of local recurrence and distant metastases. The first-line treatment for metastatic soft-tissue sarcoma has conventionally been doxorubicin-based. Recent evidence suggests that myxofibrosarcoma may be molecularly similar to undifferentiated pleomorphic sarcoma (UPS), which is particularly sensitive to gemcitabine-based therapy. The goal of this study was to evaluate the role of gemcitabine-containing regimens for the treatment of metastatic myxofibrosarcoma refractory to doxorubicin.

Methods: We retrospectively evaluated 7 consecutive cases of metastatic myxofibrosarcoma at our institution treated with gemcitabine-based therapy in the second-line setting, after progression on doxorubicin. Baseline clinical and baseline characteristics were collected. Primary endpoints were best objective response (BOR), progression-free survival (PFS), and overall survival (OS).

Results: Baseline and tumor characteristics are presented in Table 1. Median age was 66, and 43% of patients were male. The majority of patients had a performance status of 1. All patients had primary surgical resection of myxofibrosarcoma and all originated in the lower extremities. The clinical benefit rate for gemcitabine-based therapy after progression on first-line standard chemotherapy was 71% (5/7 patients), with 57% (4/7 patients) showing a radiological response. With a median follow-up of 14 months, median progression-free and overall survival were 8.5 months and 11.4 months, respectively.

Conclusion: Gemcitabine-based chemotherapy was associated with encouraging response rates in this cohort of patients with metastatic myxofibrosarcoma, similar to those seen in UPS. An implication is that gemcitabine and UPS could be studied together for novel gemcitabine-based regimens for this disease.

Table 1. Cases of metastatic myxofibrosarcoma refractory to doxorubicin treated with gemcitabine-based therapy.

	Age	Sex	ECOG	Size (cm)	Depth	Grade	Margins	Regimen	BOR	PFS	OS
Case 1	66	M	2	Unknown	Unknown	2	Unknown	Gem/docetaxel	PD	1.5 mo	2 mo
Case 2	68	M	1	16.5	Deep	3	Affected	Gem/dacarbazine	PD	5 mo	11 mo
Case 3	68	M	0	17	Deep	2	Affected	Gem	CR	8.5 mo	83 mo
Case 4	62	F	1	15	Deep	3	Affected	Gem/dacarbazine	SD	12 mo	13 mo
Case 5	67	F	1	2.6	Superficial	3	Affected	Gem/dacarbazine	PR	11 mo	13 mo
Case 6	66	F	1	14.5	Deep	3	Affected	Gem/dacarbazine	PR	4 mo	8 mo
Case 7	63	F	1	9	Deep	3	Uninvolved	Gem/dacarbazine	CR	10 mo	11 mo

Poster #137 3463019

TNT: A PHASE 2 STUDY USING TALIMOGENE LAHERPAREPVEC, NIVOLUMAB AND TRABECTEDIN AS FIRST, SECOND/THIRD LINE THERAPY FOR ADVANCED SOFT TISSUE SARCOMA, INCLUDING DESMOID TUMOR AND CHORDOMA [NCT03886311]

Sant P. Chawla[1], *Victoria Chua-Alcala*[1], *Ted T. Kim*[1], *Kelly Wang*[1], *Paul S. Dy*[1], *Nicole L. Angel*[1], *Micaela K. Paz*[1], *Ania M. Moradkhani*[1], *Doris M. Quon*[1], *Steven M. Wong*[1], *Omid Jafari*[1], *Erlinda M. Gordon*[1]
[1]*Sarcoma Oncology Center, Santa Monica, California, UNITED STATES*

Objective: Primary Objective: To evaluate progression-free survival (PFS)

Secondary Objectives: To assess (1) Best overall response during the treatment period, (2) PFS rate at 6 and 9 months, (3) OS rate at 6,9 and 12 months, (4) Incidence of conversion from unresectable to resectable tumor, and (5) Incidence of treatment-related adverse events.

Methods: Eligible patients include previously treated or untreated male or female patients ≥ 18 years of age with locally advanced unresectable or metastatic soft tissue sarcoma (STS), measurable disease by RECIST v1.1, and at least one accessible tumor for TVEC intratumoral injection. N (3 mg/kg i.v. q 2 weeks), T (1.2 mg/m2 i.v. q 3 weeks) and TVEC (1x10e8 PFU/ml q 2 weeks depending on tumor size) were administered. A test dose of TVEC (1x10e6 PFU/ml) was initially given, followed three weeks later by full dose TVEC. Primary endpoint: Progression-free survival (PFS); Secondary endpoints: (1) Best overall response during treatment period, (2) PFS rate at 6 and 9 months, (3) Overall survival (OS) rate at 6, 9, and 12 months, (4) Incidence of conversion from unresectable to resectable tumor, and (5) Incidence of treatment-related adverse events.

Results: Efficacy analysis: There were thirty-one evaluable subjects. Best Overall Response by RECIST v1.1 = 2 PR, 23 SD, 6 PD; disease control rate was 80.6%. The median PFS was 4.4 (range: 1-11) months; 6-month PFS rate: 48.0%. The median OS was 8.3 (range 1-11) months;(6-month OS: 87.5%).

Safety analysis: Grade 3 TRAEs include fatigue (n=2), decreased ejection fraction (n=1), anasarca (n=1), dehydration (n=1), decreased cortisol (n=1), anemia (n=9), thrombocytopenia (n=4), neutropenia (n=4), gastroenteritis (n=1), increased ALT (n=8), increased AST (n=1), and increased GGT (n=1). Grade 4 TRAEs observed were thrombocytopenia (n=2). There was no conversion from unresectable to resectable tumor.

Conclusion: These results suggest that combinatorial therapy with Talimogene laherparepvec, Nivolumab and Trabectedin may be (1) equal or better than standard first, second/third line therapy in achieving disease control, and (2) safer than standard therapy for patients with advanced soft tissue sarcoma with no unexpected toxicities.

Poster #138 3463040

THE PROGNOSTIC IMPORTANCE OF PATHOLOGIC FRACTURE IN LIMB SALVAGE SURGERY FOR CHONDROSARCOMA

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Objective: Pathologic fracture (PF) has long been regarded as a poor prognostic factor in patients with primary bone sarcoma, though literature pertaining specifically to chondrosarcoma is limited despite the fact that PF is one of the most common complications of this tumor. TThe purpose of this study was to determine whether the presence of PF impacts overall survival, the development of distant metastases, or local recurrence in patients who undergo limb salvage surgery with endoprosthetic reconstruction for chondrosarcoma.

Methods: 69 consecutive patients who underwent limb salvage surgery with cemented stem endoprosthetic reconstruction for chondrosarcoma of the extremity between December 1980 and December 2019 were retrospectively reviewed. The average follow-up of surviving patients was 10.4 years (range: 0.2 – 33.1 yrs). All follow-up was performed at a single institution. Patients who presented with a PF were compared to patients without a PF with regard to demographic, oncologic, procedural, and outcome data.

Results: 7 patients (10.1%) had a PF at the time of surgery. PF patients were significantly older than patients without PF (65.0 vs 50.5 years; $p<0.001$). There were more high grade IIA/IIB tumors in the PF group, while patients without PF had predominantly low grade IA/IB tumors (28.6%/71.4%/0% I/II/III vs 53.2%/40.3%/6.5%; $p=0.32$). More patients presenting with PF had dedifferentiated chondrosarcoma (42.9% vs 19.4%; $p=0.15$). 57.1% of patients with PF died of disease, compared with only 17.7% of patients without PF ($p=0.02$). Overall, disease-specific patient survival was 71.4%, 53.6%, and 26.8% at 1, 5, and 10 years, respectively, for the PF group versus 94.7%, 79.5%, and 76.3% for patients without PF ($p=0.004$) (Figure 1). 85.7% of patients with PF developed distant metastases compared with 21.0% of patients without PF ($p<0.001$). For patients with dedifferentiated chondrosarcoma, 100% of patients with a PF developed distant metastases versus only 26.3% of patients without a PF ($p<0.001$). Survival to distant metastases was significantly diminished in patients with a PF, with only 57.1% and 14.3% of patients remaining free of distant metastases at 1 and 3 years, respectively, compared with 91.3% and 77.2% of patients without PF ($p<0.001$) (Figure 2). Finally, the incidence of local recurrence was significantly higher in patients with a PF compared to patients without a PF (57.1% vs 12.9%; $p=0.003$). Only 21.4% of patients with PF were free of local recurrence at 3 years, compared with 89.7% of patients without a PF ($p<0.001$) (Figure 3).

Conclusion: The presence of a pathologic fracture in patients who undergo limb salvage surgery for chondrosarcoma is a poor prognostic factor associated with significantly decreased survival and an increased risk of both distant metastasis and local recurrence, particularly in patients with dedifferentiated disease.

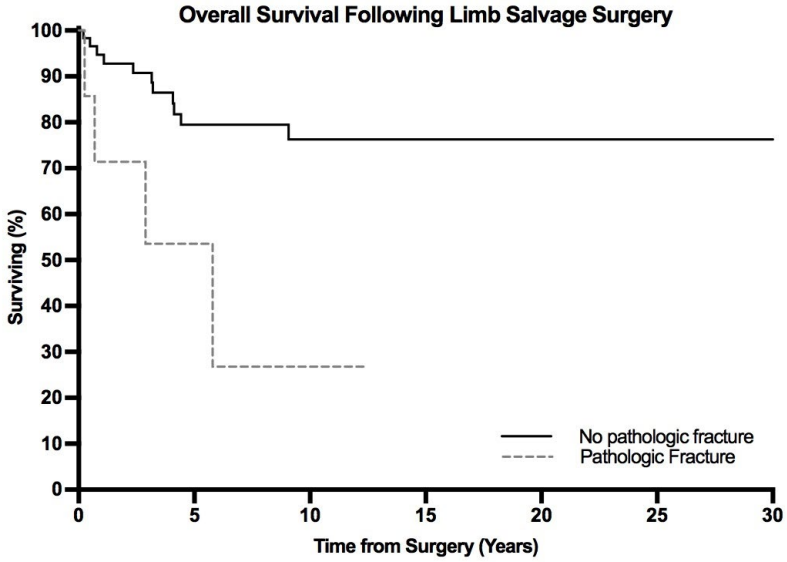

Figure 1: Disease-specific survival following limb salvage surgery for chondrosarcoma was significantly lower in patients with a pathologic fracture compared to patients without a pathologic fracture (p=0.004).

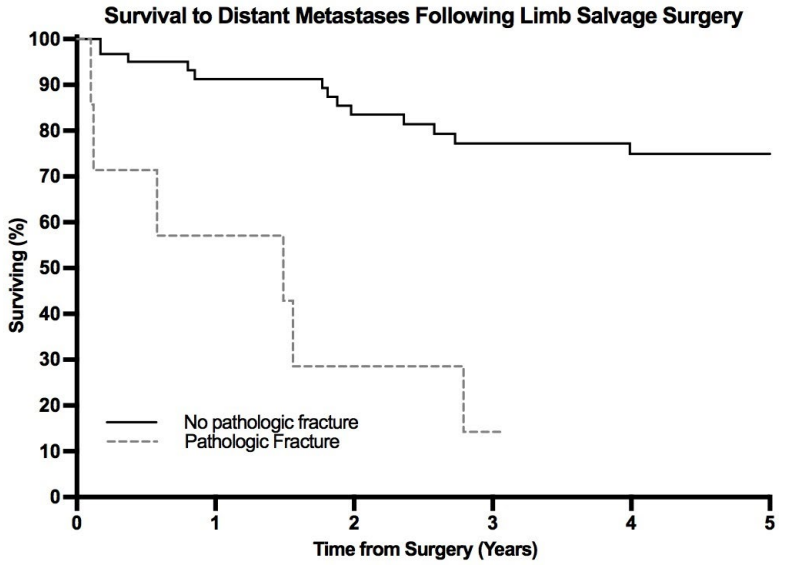

Figure 2: Following limb salvage surgery for chondrosarcoma, survival to distant metastases was significantly lower in patients with a pathologic fracture compared to patients without a pathologic fracture (p<0.001).

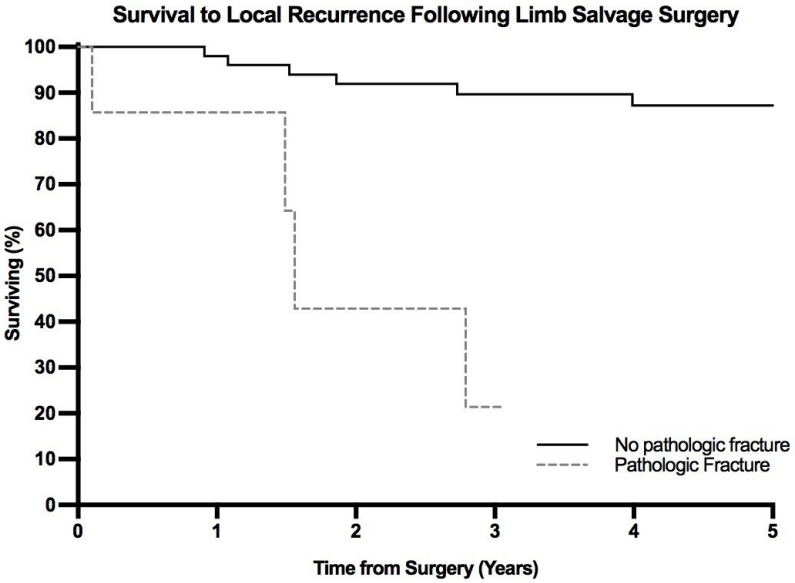

Figure 3: Survival to local recurrence following limb salvage surgery for chondrosarcoma was significantly lower in patients with a pathologic fracture compared to patients without a pathologic fracture (p<0.001).

Poster #139 3463046

ASEPTIC LOOSENING FOLLOWING LIMB SALVAGE SURGERY FOR TUMOR: A REVIEW OF 245 PRIMARY CEMENTED STEM DISTAL FEMORAL REPLACEMENTS IMPLANTED OVER A 40-YEAR PERIOD

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Objective: As survival of patients with musculoskeletal tumors continues to improve, aseptic loosening (AL) has become a leading cause of failure of endoprosthetic reconstruction, particularly for distal femoral replacements (DFR). The objective of this study was to describe the incidence of AL and to identify modifiable risk factors for its development.

Methods: A retrospective review was performed of 245 consecutive primary, cemented stem DFRs implanted for oncologic diagnoses over a 40-year period. Demographic, radiographic, oncologic, procedural, and outcome data was collected and analyzed. The primary outcome of interest was implant failure secondary to AL, defined as the need for major revision surgery or amputation. A multivariate analysis was performed to identify risk factors for AL, followed by 1:1 matching for age, sex, resection length, and implant modularity. Implant survival to AL was compared using Kaplan-Meier analysis.

Results: 33.5% of implants failed (82/245). AL and structural failure were the most common causes of implant failure, both with an incidence of 11.8% (29/245) (Table 1, Figure 1). Median time to AL was 8.7 years. Younger age (p=0.002), male sex (p=0.01), longer resection length (p=0.04), and non-modular implants (p=0.002) were all significantly associated with the development of AL (Table 2). When controlling for these factors, stem tip location in metaphyseal bone was independently associated with AL (p=0.04). 36% of implants that loosened had a stem tip located in the metaphysis, versus only 8% of implants that did not fail. For implants with a metaphyseal stem tip, survival to AL was 72.7%, 45.5%, and 22.7% at 5, 15, and 30 years, respectively, versus 84.6%, 71.2%, and 47.6% for implants in which the stem tip was located in the diaphysis (Figure 2).

Conclusion: As an ever-increasing number of patients are able to outlive their endoprosthetic reconstructions, most patients who undergo limb salvage surgery will require at least one major revision surgery during their lifetime. Stem extension into metaphyseal bone was associated with diminished survival to AL, which was found to be the most common cause of failure of cemented stem DFRs. This should be taken into consideration when preoperatively planning endoprosthetic reconstruction.

Table 1: Modes of failure for cemented distal femoral replacements

Mode of Failure	Incidence (n)	Median Time to Failure (yrs)
Soft Tissue Failure	0.4% (1/245)	0.4
Aseptic Loosening	11.8% (29/245)	8.7 (range: 0.8 - 33.6)
Structural Failure	11.8% (29/245)	8.4 (range: 0.5 - 22.6)
Infection	5.3% (13/245)	2.0 (range: 0.07 - 7.8)
Tumor Progression	4.1% (10/245)	1.3 (range: 0.05 - 6.7)
Total	33.4% (82/245)	4.1 (range: 0.05 - 33.6)

Table 2: Risk factors for aseptic loosening of cemented stem distal femoral replacements

	Aseptic Loosening (n=29)	No Failure (n=163)	P-Value
Age (yrs)*	21.0 (17.3 - 24.7)	28.5 (25.9 - 31.1)	0.002
Sex (M/F)(%)	79.3/20.7	54.0/46.0	0.01
Resection Length (cm)*	20.3 (17.7 - 22.9)	17.3 (16.5 - 18.1)	0.04
Stem Length (cm)*	13.0 (12.1 - 13.9)	12.7 (12.4 - 13.0)	0.54
Stem Width (mm)*	14.0 (13.1 - 14.9)	13.5 (13.2 - 13.8)	0.32
Implant Modularity (N/Y)(%)	69.0/31.0	36.8/63.2	0.002
Follow-Up (yrs)*	21.4 (18.0 - 24.8)	6.5 (5.3 - 7.7)	<0.001

*Mean (95% Confidence Interval)

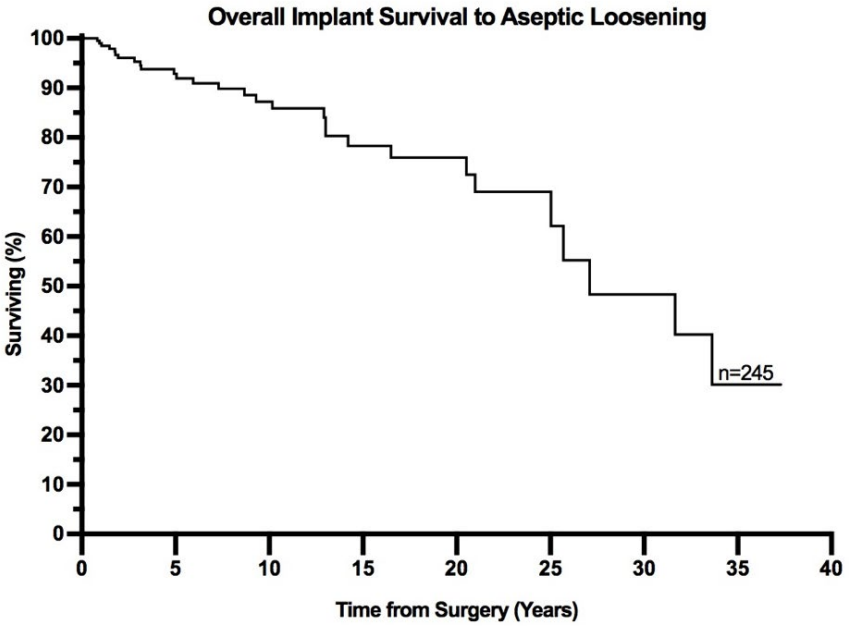

Figure 1: Kaplan-Meier curve representing overall implant survival with revision surgery for aseptic loosening as the endpoint.

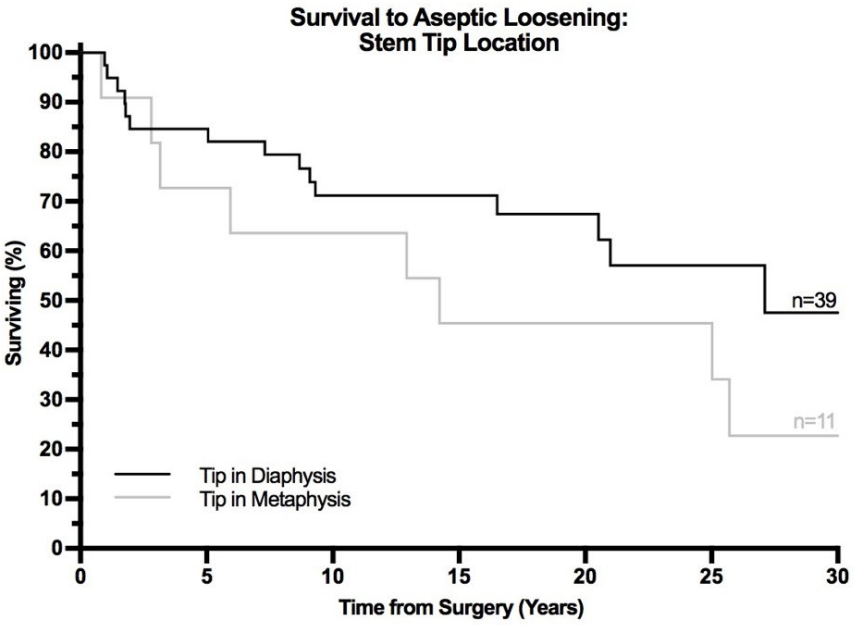

Figure 2: Survival to aseptic loosening by stem tip location. Implants with a stem tip ending in metaphyseal bone had decreased survival compared with implants with a stem tip ending in diaphyseal bone (p=0.11).

Poster #140 3463093

THE OUTCOMES AND PROGNOSTIC FACTORS IN PATIENTS WITH OSTEOASRCOMA ACCORDING TO AGE* A JAPANESE NATIONWIDE STUDY WITH FOCUSING ON THE AGE DIFFERENCES

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Objective: There are two peaks of incidence in those aged 15 to 19 and over the age of 65. Few reports have described clinical features, prognosis and prognostic factors of osteosarcoma patients according to age.

Methods: Using the Bone and Soft Tissue Tumor Registry in Japan, we identified 1043 osteosarcoma patients including 760 who were younger than 40 years, 173 aged between 41 and 64 years, and 110 patients older than 65 years. We extracted data on patient demographics and prognosis. Prognostic factors for patients older than 65 years or other age groups were analyzed.

Results: Patients older than 65 years showed a significantly higher proportion of tumors arising in the trunk and with metastasis at diagnosis, and their 5-year disease-specific survival (DSS) rate was 32.7%. Multivariate analysis showed that the presence of metastasis at diagnosis [hazard ratio (HR): 3.04; 95% confidence interval (CI), 1.63-5.69; $P < 0.001$] and tumors > 16 cm in size (HR: 2.84 compared with < 8 cm; 95% CI, 1.16-6.97; $P = 0.023$) were significantly associated with worse disease specific survival (DSS). The 5-year DSS was 39.1% in 80 patients older than 65 years without metastasis at diagnosis. Methotrexate was used in only 5.0% of these patients. Adjuvant chemotherapy was not significantly associated with better DSS ($P = 0.323$) in this generation and aged between 41 and 64 years ($P = 0.566$), although adjuvant chemotherapy yielded significantly better survival in patients younger than 40 years ($P < 0.001$).

Conclusion: Analysis of this cohort of osteosarcoma patients revealed unique clinical, therapeutic and prognostic features according to age groups in the largest cohort. Adjuvant chemotherapy was not associated with a better DSS in the group of patients aged between 41 and 64 years or older than 65 years.

Poster #141 3463134

COMBINING SHELF OSTEOTOMY WITH PROXIMAL FEMORAL RECONSTRUCTION AFTER ONCOLOGIC RESECTION

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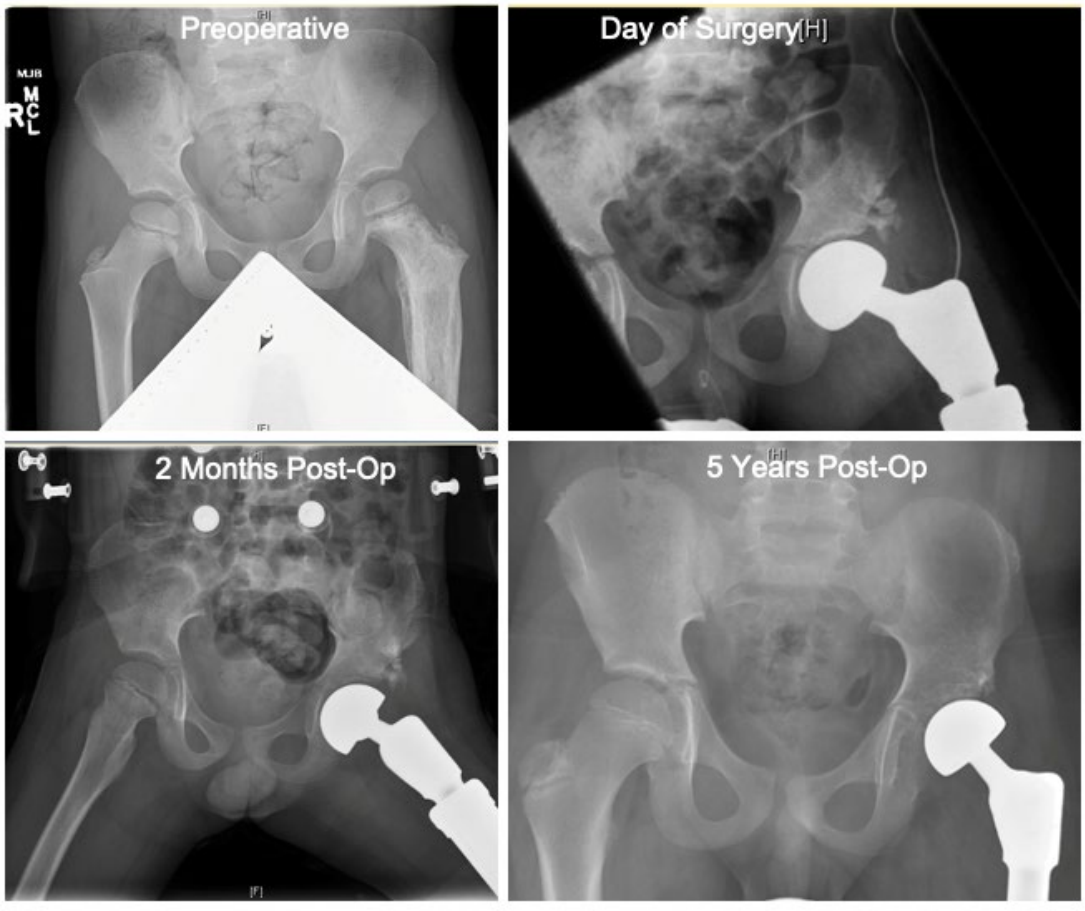
Objective: Oncologic proximal femoral resection and reconstruction (PFR) in skeletally immature children remains a formidable task due to the risk of developing acetabular dysplasia and hip subluxation with patient growth or interval leg lengthening through the prosthesis. Shelf pelvic osteotomy increases femoral head coverage and containment, and favorable long-term results have been reported in the setting of developmental dysplasia of the hip and Perthes disease. Here, we studied the outomes of a new surgical technique that combines shelf osteotomy with expandable endoprosthesis for proximal femoral reconstruction in pediatric limb-sparing surgery.

Methods: The authors performed an outcomes analysis of surgical technique of three surgeons at two centers. Patients who received PFR with shelf osteotomy over an 8-year period were included in this study. Data were collected retrospectively evaluating operative technique, radiographic measurements of acetabular depth and skeletal maturity, complications including dislocation, subluxation, periprosthetic fracture, and radiographic outcomes.

Results: Five skeletally immature patients ages 4-12 with open tri-radiate cartilages underwent PFR with shelf osteotomy during this study period (2012-2020). Mean follow up was 2.7 years (range 2 weeks-7 years). Mean (standard deviation) lateral center edge angle (LCEA) status post PFR-shelf osteotomy was 33.5 (+/- 12.5) There were no reported incidences of subluxations, dislocations, periprosthetic fractures, or soft tissue complications. The three patients with the longest follow up showed earlier triradiate cartilage closure in the operative PFR side compared to the non-op side. All patients have been able to return to independent ambulation, and the two patients with longest follow up at 5 and 7 years tolerated serial 6 lengthenings, 7.25cm total; and 6 lengthenings, 6.5cm total, respectively. Case example with radiographs at pre-operative, day of surgery, two months post-operatively, and 5 years post-operatively are shown below (Figure 1).



Conclusion: Combining PFR with shelf osteotomy is a surgical technique in limb salvage pediatric orthopaedic oncology that may help to decrease complications of subluxation, dislocation, and periprosthetic fracture with serial lengthening and patient growth.

Poster #142 3463148

COMPREHENSIVE MASSIVELY PARALLEL SEQUENCING OF SARCOMAS: EXPERIENCE FROM AN AUSTRALIAN TERTIARY HOSPITAL LABORATORY AND STATE SARCOMA SERVICE

Daniel Wong[1], *Tindaro Giardina*[1], *Cleo Robinson*[1], *Marc Thomas*[1], *Timothy Humphries*[2], *Peter Robbins*[1], *Anne Long*[2], *Michael Millward*[2], *Richard Carey-Smith*[3], *Benhur Amanuel*[1]
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Objective: The role and utility of massively parallel sequencing (MPS; also called next-generation sequencing) for patients diagnosed with sarcomas in routine clinical practice is still being defined. The aim of this study was to review all sarcomas tested by MPS in our Department and as part of the Western Australian State Sarcoma Service to identify common indications for testing and the frequency of significant findings affecting diagnosis and management.

Methods: All cases tested on the Illumina TruSight Tumor (TST) 170 MPS platform from 2018 to the present were retrospectively identified from our laboratory database. The TST170 platform is a comprehensive targeted hybrid capture-based assay which analyses DNA and RNA to detect cancer-related small variants, amplifications, splice variants and fusions, including common sarcoma-related fusions. Data collected from all cases included patient age, gender, tumour site, pathological diagnosis, clinical indication for molecular testing by MPS, molecular findings and any novel therapeutic options/potential clinical trials proposed based on these findings.

Results: Fifty-four (54) cases were identified comprising 29 (54%) females and 25 (46%) males with median age of 53 years (0.8 – 80 years). The most common diagnoses were undifferentiated sarcoma (n=9, 17%), leiomyosarcoma (n=6, 11%), angiosarcoma (n=5, 9%), Ewing sarcoma (n=4, 7%) and dedifferentiated liposarcoma (n=4, 7%). Indication for testing was for identification of targetable molecular alterations in metastatic disease in 29 (54%), in locally advanced/recurrent disease in 22 (40%) and for refinement of diagnosis in 3 (6%). Molecular alterations were identified in 49 (91%) cases, including single nucleotide variants in 39 (72%), copy number variants in 23 (43%) and fusions in 15 (28%). Of the latter, 6 were recognised drivers and 9, novel or possible passenger fusions. Two driver fusions were unanticipated, leading to refinement in diagnosis (*EWSR1-CREB1* changing malignant myoepithelioma to malignant angiomatoid fibrous histiocytoma; *EWSR1-ETV4* changing *NUT*-rearranged sarcoma to Ewing sarcoma). Potential novel therapies and clinical trials were suggested 44 (81%), including 4 with *ALK* and/or *NTRK* isoforms.

Conclusion: In this cohort of sarcomas, the most common clinical indication for molecular testing by MPS was for identification of targetable molecular alterations in metastatic and locally advanced/recurrent disease (rather than for confirmation or refinement of pathological diagnosis). Molecular alterations were identified in >90%, most frequently single nucleotide variants. Changes to the original pathological diagnosis occured in only 2 (4%) cases. Potential novel therapies and clinical trials were suggested in the majority (81%) based on the findings, including *ALK* and/or *NTRK* isoforms which might respond to highly targeted therapy. However, further study is required to determine how frequently actual changes to clinical management and enrollment in proposed clinical trials occurred.

Poster #143 3463161

TARGETING CYCLIN DEPENDENT KINASE 8 IN FUSION POSITIVE RHABDOMYOSARCOMA

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Objective: Rhabdomyosarcoma (RMS), a cancer with features of skeletal muscle, is the most common soft-tissue sarcoma of childhood. The fusion positive variant (FP-RMS), previously named alveolar RMS, is particularly difficult to cure, with a five-year survival of <50%. In the majority of cases, FP-RMS is characterized by t{2;13) resulting in expression of the PAX3-FOXO1 fusion protein, a "super transcription factor" with the binding specificity of PAX3 but the transactivational power of FOXO1. In the metastatic setting, *PAX3-FOXO1* positive patients have a four-year survival of <10%.

Since PAX3-FOXO1 is not currently druggable, we are searching for proteins that interact with PAX3-FOXO1 that are more amenable to pharmacologic inhibition. To this end, we performed two separate but complementary screens: a BirA proximity labelling proteomics screen and a pharmacologic counter-screen to prioritize the proteomics hits. From these results, we identified cyclin dependent kinase 8 (CDK8), a critical component of a large protein assembly known as the Mediator complex that enables physical looping of genomic enhancer regions with transcriptional start sites. We aim to understand how CDK8 contributes to RMS, investigate the value of CDK8 as a therapeutic target in vitro, and assess the pre-clinical efficacy of CDK8 loss of function (LOF) or inhibition (CDK8i) in vivo.

Methods: To assess the impact of CDK8 LOF on FP-RMS cell oncogenic phenotypes, we will stably express CDK8 shRNAs in FP-RMS cells and evaluate proliferation, apoptosis, differentiation, and stemness. Flow cytometry and reporter assays will assess the impact of CDK8 shRNAs on cell cycle and PAX3-FOXO1 transcriptional power, respectively. To investigate the value of CDK8 as a therapeutic target in vitro, we will examine CDK8 expression in human RMS tissue microarrays via IHC, and perform in vitro MTT assays of CDK8i in FP-RMS cells using available small molecule inhibitors of CDK8. To assess the pre-clinical efficacy of CDK8 LOF, we will test the impact of conditionally (dox-inducible) expressed CDK8 shRNAs, or the most effective CDK8 pharmacologic inhibitor determined from our in vitro MTT assays, in FP-RMS tumor xenografts. Xenografts will be examined for CKD8 target inhibition, and for mechanisms of inhibition of tumorigenesis including IHC assays for inhibition of proliferation (Ki67), induction of apoptosis (TUNEL), and induction of myogenic differentiation (MYOD1/myogenin staining).

Results: Thus far, we have found that genetic inhibition of CDK8 via RNAi, as validated by RT-qPCR and immunoblotting, inhibits growth of human FP-RMS cells in vitro, in part through induction of myogenic differentiation. Pharmacologic inhibition of CDK8 via the small molecule senexin A induces cytotoxicity with an IC50 in the 100-200nM range. Efforts are ongoing to complete the remaining in vitro phenotypic assays and in vivo xenograft assays.

Conclusion: This work is beginning to establish evidence for targeting CDK8 in FP-RMS.

Poster #144 3463166

CLINICAL BENEFIT WITH RIPRETINIB AS ≥4TH LINE TREATMENT IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR: UPDATE FROM THE PHASE 3 INVICTUS STUDY

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Objective: Ripretinib is an FDA-approved switch-control tyrosine kinase inhibitor (TKI) that broadly inhibits mutant KIT and PDGFRA kinase signaling. In the INVICTUS study (NCT03353753), a phase 3 randomized, double-blind, placebo-controlled trial in ≥4th-line advanced gastrointestinal stromal tumor (GIST), ripretinib compared with placebo significantly improved progression-free survival (PFS, 6.3 vs. 1.0 months) reducing the risk of disease progression or death by 85% and showed a clinically meaningful improvement in overall survival (OS, 15.1 vs 6.6 months); data as of May 31, 2019 (ESMO, 2019). Ripretinib is associated with a well-tolerated safety profile. Here, we report the updated results with an additional 9 months of follow-up.

Methods: Patients with advanced GIST previously treated with at least imatinib, sunitinib, and regorafenib were randomized (2:1) to ripretinib 150 mg QD or placebo. Upon disease progression determined by blinded independent central review (BICR), patients on placebo could cross over to ripretinib 150 mg QD. All patients who received 150 mg QD and progressed radiographically could receive 150 mg BID. Updated PFS by BICR, OS, and safety are reported here with data as of March 9, 2020.

Results: Overall, 129 patients were randomized and 128 received treatment (ripretinib 150 mg QD, n=85; placebo, n=43). Patients randomized to ripretinib had a median PFS of 6.3 (95% CI 4.6–8.1) vs. 1.0 (95% CI 0.9–1.7) months for patients on placebo with a hazard ratio (HR) of 0.16. The median OS in the ripretinib arm was not reached (95% CI 13.1–NE) vs. 6.3 (95% CI 4.1–10.0) months in the placebo arm with a HR of 0.43. No new safety concerns emerged with longer exposure to ripretinib.

Conclusion: With a cut-off date for analysis approximately 9 months after the primary results, this evaluation of median PFS and OS in the phase 3 randomized INVICTUS trial showed an improvement in the median OS benefit in the ripretinib arm from 15.1 months to not reached (95% CI 13.1 –NE) and a similar median PFS of 6.3 months in the ripretinib arm. These updated results confirm the clinically meaningful benefit in PFS and OS for ripretinib with a well-tolerated safety profile in patients with advanced GIST treated with at least 3 prior TKIs, including imatinib.

Poster #145 3463185

INCIDENCE OF SARS-COV-2 IN PEDIATRIC ONCOLOGY CLINIC AT THE EPICENTER OF THE PANDEMIC

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Objective: Cook County, Illinois, the home of Rush University Medical Center, had the U.S peak COVID-19 rates in April and May of 2020,[i] creating tension between the risks of timely and life-saving therapy and coming into the pediatric oncology clinic. Corresponding to the "Shelter-in-Place" order in Chicago (3/13/2020 – 6/13/2020), all possible pediatric oncology hospital/clinic visits were canceled. However, for many patients (such as pediatric oncology patients), receiving life-saving therapy, visits couldn't be deferred.

[i] https://coronavirus.jhu.edu/us-map

Methods: Chart reviews of all patients who came to our clinic/hospital for care during the "shelter period" identified COVID-19 nasal swab and SARS-CoV-2 IgG results. A positive test was defined as a single positive COVID-19 nasal swab or an IgG antibody detected from 14 days after the start of the "Shelter-in-Place" to 14 days after in the absence of a positive COVID swab. A negative was defined as a negative swab more than a week after a previous negative or a negative antibody test. Data from the Chicago Department of Public Health and Rush Internal Data, the author's home institution, was used for comparison for the same time period.

Results: During the shelter period, there were 164 visits to the pediatric oncology office and 54 patients with an average of 4.8 patients in the infusion room per day, 3.2 visits to the pediatric oncology office per patient, and 4.2 total clinic encounters per patient. There were 3 positive tests of 96 tests performed (3.1%) in 40 patients (7.5%) with 214 total patient encounters (1.4%). There was 1 positive patient out of 26 patients tested in the ages 0-17 category (3.9%), and 2 positive patients out of 14 tested in the ages 18-29 category (14%). In the 54 patients who visited the pediatric oncology infusion room, office, or were a part of the clinic ages 0-29, 51 were immunocompromised (94%) including 27 on active immunosuppressant treatment (50%). The percentage of positive COVID-19 cases for ages 0-17 was 3.9% and 14% for ages 18-29 compared to 17% and 20%[ii] in Chicago citywide and 5% (ages 0-17) and 8% (ages 18-24) at Rush Hospital overall. The percentage of positive COVID-19 cases for ages 0-29 was 19% for Chicago Citywide and 7.5% for the Rush pediatric oncology patients.

[ii] https://app.powerbigov.us/viewr=eyJrIjoiYjUwNjEwN2QtYmJkYS00MTZmLTg4YjMtZGRkMzEzMmFmYjg4IiwidCI6Ijcw-MzZjZGE5LTA2MmQtNDE1MS04MTQ0LTk3ZGRjNTZlNzAyNyJ9

Conclusion: The positive COVID-19 cases in our pediatric oncology clinic during the shelter period was significantly lower for ages 0-29 ($p = 0.0287$) and ages 0-17 ($p = 0.0438$) than the Chicago citywide data during the peak period of the pandemic. The positive COVID-19 cases for ages 18-29 also presented lower than the citywide data with 2 positive cases for 14 patients tested but did not appear to be statistically significant most likely due to the small sample size ($p = 0.4518$). The positivity percentage for all ages of pediatric oncology patients was lower than the total Rush Hospital positivity percentage as well.

We infer that overall, our vulnerable patients were using successful measures for preventing the disease acquisition, such as isolation, distancing, masks, and hand washing. The content on this abstract supports that vulnerable pediatric patients can be protected without deferring their treatment.

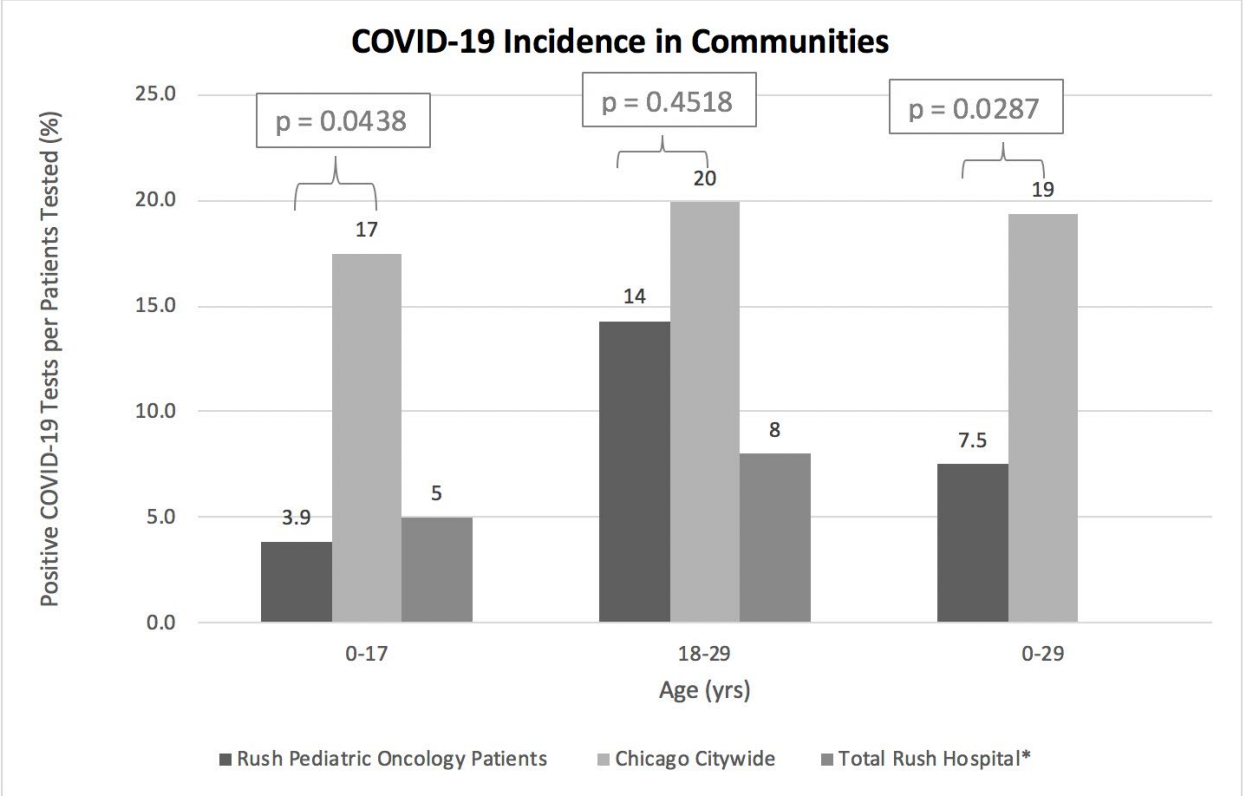

Figure 1: *Rush Hospital data uses ages 0-17 and ages 18-24. Chicago citywide data obtained from Chicago Department of Public health. The percent positivity is defined as: $\frac{\text{positive patients}}{\text{total patients tested}} \times 100\%$. The p-values are obtained for the Rush Pediatric Oncology Data and Chicago Citywide Data.

Poster #146 3463241

DEDIFFERENTIATION WITHIN A WELL DIFFERENTIATED LIPOSARCOMA OF THE EXTREMITY OR TRUNK – IMPLICATIONS FOR CLINICAL MANAGEMENT

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Objective: Low grade, well differentiated (WD) liposarcoma can commonly occur in the extremities or trunk; presence of a high grade, dedifferentiated (DD) component is rare. In contrast to liposarcoma in the retroperitoneum, in which DD is more common, the clinical implications of DD in the extremity or trunk are not as clear. In this study, we sought to 1) characterize patients with extremity or trunk WD / DD liposarcoma, 2) define overall survival (OS) and incidences of local recurrence (LR) and distant metastasis (DM), and 3) explore potential predictors of outcome.

Methods: Retrospective clinicopathologic data were collected from a single, high-volume sarcoma referral center for eligible patients who underwent treatment including surgery from 2009-2019. All tumors were required to have evidence of MDM2 expression (IHC, FISH) to confirm the diagnosis and rule out lipoma. Standard descriptive methods were used and comparisons were assessed based on standardized mean difference (SMD). OS was estimated using the Kaplan-Meier method and compared with the log-rank test. Cumulative incidence curves of first events (LR and DM) were calculated in a competing risk framework and compared with the Gray test. Firth's penalized Cox univariable models were performed to assess the association between OS and clinicopathologic features. Fisher Exact test was performed to assess the association between frequencies of LR in DD subgroups in primary and recurrent disease groups.

Results: In total, 210 (148 primary, 62 recurrent) patients were included in this study. Tumors with DD were more common in recurrent versus primary disease (39 vs. 22%, SMD = 0.362). Median total tumor size and size of the DD component were larger in primary (15.0 and 7.5 cm) compared to recurrent (9.0 and 5.0 cm, SMD = 0.940 and 0.569) disease; however the median percentage of DD within each tumor was slightly higher at recurrence (100 vs. 78.9%, SMD = 0.349). All patients underwent complete resection with a median follow-up of 50.9 months. During the study period, for the entire cohort (WD, DD), there were 20 patients with LR (9.5%), 5 with DM (2.4%), and 10 patients who died (4.8%). In primary disease, all recurrence events (LR or DM) except one (LR) were in patients with DD tumors; as expected, worse OS was observed for patients with DD versus WD ($p < 0.001$). In recurrent disease, the incidences of LR were similar in patients with WD and those with DD ($p = 0.559$). No patients developed DM, however, worse OS persisted in patients with DD versus WD ($p = 0.011$). On univariable modeling for the entire cohort, worse OS was associated with age ($p = 0.041$), DD component size ($p = 0.036$) and higher grade ($p < 0.001$). There was no association between receipt of radiation or chemotherapy and OS. Due to the low number of events, further multivariable (adjusted) analysis was not feasible. Subgroup analysis of patients with DD suggested a higher frequency of LR in grade 3 versus 2 in primary (5/12 vs. 1/21, $p = 0.016$) but not recurrent (1/4 vs. 2/20, $p = 0.437$) disease.

Conclusion: The presence of DD in the extremity or trunk suggests a biologic change in the tumor leading to significantly worse clinical outcome in both primary and recurrent disease. However, the risk of local recurrence and distant metastasis are lower and overall survival is higher compared to what is typically observed for its counterpart in the retroperitoneum. The size and grade of the DD component in itself may have implications to guide clinical management. While surgery remains the mainstay of treatment; better adjunct therapies are needed particularly for patients with DD.

Poster #147 3463247

LOCAL RECURRENCE OF SOFT TISSUE SARCOMA REVISITED: IS THERE A ROLE FOR "SELECTIVE" RADIATION?

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Objective: Soft tissue sarcomas (STS) are uncommon tumors of mesenchymal origin with extremities being the most often affected locale. In recent decades multimodal treatments for STS have become standard, with combination surgery and external radiation treatment used together to improve local control and patient survival. Certain prognostic factors, such as positive surgical margins, are associated with an increased risk of local recurrence. Perioperative radiation is generally utilized when a high-grade soft tissue sarcoma is removed with close or positive margins. However, there are occasional clinical situations, such as delayed wound healing, the perception of adequate margins, or patient preferences, where treatment is with surgical excision alone. The primary aim of this project was to determine the local recurrence rate of soft tissue sarcoma which would have met criteria to receive perioperative radiation, but were not treated with radiation. We compared the local recurrence rate to similar cases that were treated with pre or postoperative radiation therapy (XRT). Secondarily, we sought to further elucidate any associations between local recurrence and tumor histology, margins, size, or grade in the group of patients who did not receive radiation.

Methods: Data were collected via EPIC electronic medical record chart review and categorized according to patient demographics, survival, procedure date, procedural complication, tumor type, size, grade, nearest resection margin, concurrent metastasis, recurrence, survival, and whether or not radiation treatment was received. Inclusion criteria were patients 18 years or older with diagnosis of a primary (nonrecurrent) grade 2/3 or 3/3 STS who presented for initial resection or tumor bed re-excision between September 1, 2010 and May 8, 2019. We used time-based survival measurements for local recurrence and log rank testing for measures of association.

Results: We identified 166 patients who met inclusion criteria. For the entire cohort, there were 18 local recurrences (LR) (10.8%). Eighty-two patients (49.4%) did not receive perioperative XRT. Of these, 14 (17.1%) recurred compared to 4/84 (4.8%) of those treated with XRT (p=0.001). For patients not treated with XRT, there were increased incidences of local recurrence in older age groups, myxofibrosarcoma, positive margins, and prior attempts at excision (Table 1). Myxofibrosarcoma accounted for 33 (19.9%) cases and 12 (66.7%) local recurrences.

Conclusion: The overall local control rate in high-grade STS without use of adjuvant XRT in this cohort was 82.9%. In certain circumstances, treatment with a negative margin surgical resection followed by observation is appropriate. However, higher rates of local recurrence were seen in myxofibrosarcoma, resections with positive margins, and tumor-bed re-excisions. In these circumstances, the addition of radiation or a wider excision may be warranted.

Table 1. Local recurrences in patients treated without radiation

	Recurrence	No recurrence	p value
Histology			
Leiomyosarcoma	0	14	0.995
Liposarcoma	0	3	0.997
Myxofibrosarcoma	11	13	0.038
Synovial sarcoma	0	3	0.997
UPS	1	16	0.927
Other	2	22	Ref
Grade			
High (3/3)	9	54	0.776
Intermediate (2/3)	5	28	
Size			
<5 cm	9	38	0.475
5-10 cm	3	21	
>10 cm	2	23	
Depth			
Superficial	8	39	0.760
Deep	6	43	
Prior surgery			
Yes	9	30	0.046
No	5	52	
Margins			
R0 - wide, marginal	9	71	0.020
R1 - intralesional	5	11	

Poster #148 3463515

A NOVEL METHOD FOR THREE-DIMENSIONAL GROWTH AND ASSAY OF PAX3-FOXO1 FUSION-POSITIVE RHABDOMYOSARCOMA CELLS ENRICHES IN CANCER STEM CELL CHARACTERISTICS

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Objective: The development and optimization of three-dimensional cell culture techniques over the last several years has been an important tool for the study of carcinomas. These model systems have been used to examine properties of cancer cell stemness, including multipotency, increased tumorigenicity and metastatic potential *in vivo*, and chemoresistance. Moreover, these three-dimensional cell culture systems represent an intermediate model system that partially bridges the gap between two-dimensional adherent cell culture techniques and *in vivo* xenograft assays. Recently, methods to grow and assay Ewing's sarcoma, osteosarcoma, liposarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, fibrosarcoma, synovial sarcoma, and fusion-negative rhabdomyosarcoma have been described. However, a clear method to culture and assay PAX3-FOXO1 fusion-positive rhabdomyosarcoma (FP-RMS) has been lacking, slowing efforts to identify the dysregulated pathways that may underlie FP-RMS stemness and metastasis.

Methods: Here, we identify key stem cell markers in human RMS tumors and cell lines and identify those most relevant to FP-RMS. We then describe a method to grow FP-RMS cell lines as spheres enriched for canonical stemness markers and assay these spheres for differences in functional stemness as compared to cells grown as adherent monolayers. Cells previously grown as spheres are subjected to differentiation-inducing conditions down myogenic, adipogenic, osteogenic, and neurogenic lineages and compared to cells previously grown as adherent monolayers. Expression of stem markers prior to differentiation and lineage-specific terminal differentiation markers after differentiation are compared. To assay tumorigenicity, cells previously grown as spheres or adherent monolayers are serially diluted and injected as xenografts. Chemoresistance of cells previously grown as spheres or adherent monolayers is determined by colony-forming assays *in vitro*.

Results: We show that FP-RMS rhabdospheres have increased expression of the stem cell markers *SOX2*, *POU5F1 (OCT4)*, and *NANOG*, and that these cells are increased in their propensity for multipotent differentiation, increased tumorigenicity *in vivo*, and chemoresistance. Finally, we demonstrate the utility of this culture method to validate and characterize new cell lines and genetic perturbations with newly developed murine tumor-derived FP-RMS cell lines.

Conclusion: This method describes a novel practical tool to support research into FP-RMS stemness, metastasis, and chemoresistance signaling mechanisms.

Poster #149 3463549

ARID1A DELETION ENHANCES OSTEOSARCOMAGENESIS IN HUMAN CELL LINES AND MURINE MODEL

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Objective: Osteosarcoma is the most common pediatric bone cancer. Although aggressive chemotherapy combined with surgery has reversed the dismal outcomes in osteosarcoma patients, survival has remained unchanged in the last 40 years. Recurrence and resistance are still seen in ~30% of osteosarcoma patients. The mechanism that drives this aggressive subtype in osteosarcoma is unclear. To address this gap in knowledge, we used a random mutagenesis screen in mice to identify mutations that enhanced the aggressive phenotype. Our objective was to identify mutations that enhance the aggressive phenotype in osteosarcoma.

Methods: Initially, an unbiased forward genetic screen using the transposon *piggyBac* was introduced to a transgenic mouse model of osteosarcoma that already exhibited conditional baseline deletions *p53* and *Rb1* driven by the *OsterixCreERT2* allele in osteoblasts. Kaplan-Meier survival analysis was performed between cohorts with and without the piggyBac transposon. Splinkerette PCR and Ion Torrent sequencing was performed to identify the most commonly mutated genes. Arid1a-floxed mice were combined with the osteosarcoma mouse model to validate *Arid1a* as a tumor suppressor gene. Additionally, human osteosarcoma cell lines with endogenous expression of ARID1A were selected for CRISPR-Cas9 gene editing to knock out *ARID1A* by targeting exon 2. Mice were anlalyzed for survival and tumor burden between cohorts with and without Arid1a. Cell lines were assessed by proliferation and migration assays to determine the impact of the loss of *ARID1A*.

Results: In the forward genetic screen, we analyzed survival of the mice with and without the transposon *piggyBac*. Mice with the *piggyBac* allele demonstrated worse survival by 5.1 months (P value < 0.0001). From the *piggyBac* cohort, we extracted 88 tumors from 38 mice and sectioned and stained tumors to observe their histology. These tumors demonstrated classic H & E osteosarcoma histology. Ion Torrent DNA sequencing identified *Arid1a* as the most frequently disrupted gene.

To validate the transposon-mediated forward genetic screen, we used *both in vitro* and *in vivo* approaches to study the effects of *Arid1a* in osteosarcoma. For the *in vitro* approach, we first selected two cell lines based on higher *ARID1A* mRNA expression compared across several osteosarcoma cell lines. We confirmed that SJSA-1 and U2-OS expressed endogenous mRNA and protein for ARID1A. We next genetically disrupted *ARID1A* with CRISPR-CAS9. Targeted deletion of exon 2 in ARID1A resulted in decreased RNA expression as detected by qRT-PCR. The consequence of deleting *ARID1A* in these cell lines was a more proliferative and migratory cell behavior.

To complement our *in vitro* approach, we bred mice with the *Arid1*$^{fl/fl}$ conditional allele with our existing *OsxCre*$^{ERT2+/-}$*;p53*$^{fl/fl}$*;Rb1*$^{fl/fl}$ transgenic osteosarcoma model. We evaluated for a more aggressive phenotype by measuring survival, total number of tumors per mouse, and metastatic burden. We analyzed three different cohorts of the *Arid1a* allele: control (*Arid*$^{wt/wt}$), heterozygous (*Arid1*$^{fl/wt}$), and homozygous (*Arid1*$^{fl/fl}$), all with the genetic background of *OsxCre*$^{ERT2+/-}$*;p53*$^{fl/fl}$*;Rb1*$^{fl/fl}$. We found that the loss of one copy of *Arid1a* significantly enhanced the progression towards morbidity by 5.5 months (166 days) and an additional 0.8 months (24 days) in the *Arid1a* homozygous deletion mice (P value < 0.0001). Furthermore, upon necropsy or microCT scanning, mice with heterozygous or homozygous deletion of *Arid1a* exhibited higher numbers of tumors per mouse. We observed on average 1.5 tumors per mouse in the *Arid1a* wildtype cohort and >4 tumors per mouse on average for the other two *Arid1a* deleted cohorts.

Conclusion: From this data, absence of *Arid1a/ARID1A* has demonstrated a more aggressive phenotype as evidenced by the more proliferative and migratory human cells and transgenic mice with lower survival and more tumor burden when *Arid1a* is deleted in osteosarcoma.

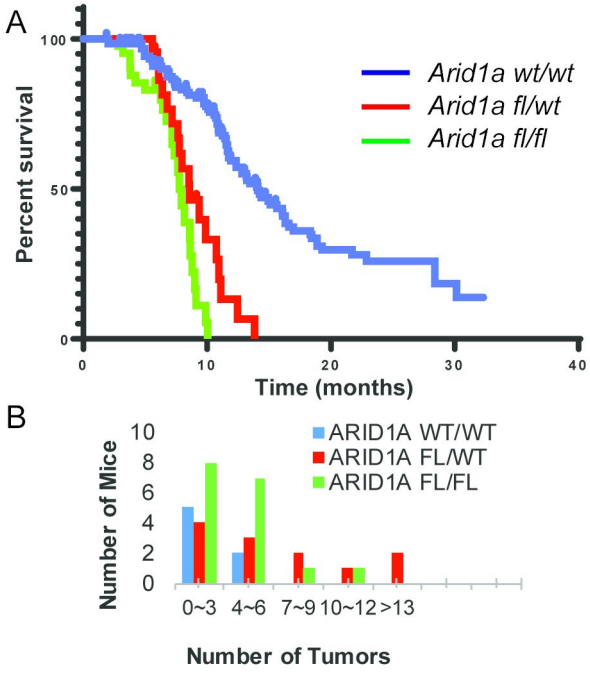

Figure 6. Impact of *Arid1a* deletion on mouse survival with osteosarcoma. (A) Kaplan-Meier Survival curve of mice with the baseline mutations of Tp53fl/fl;Rb1fl/-fl;OsxCreERT2 and varying degrees of Arid1a deletion: Arid1a wt/wt (n = 140), Arid1a fl/wt (n = 22), Arid1a fl/fl (n = 41); P-value < 0.0001 by Mantel-Cox Log Rank Test. (B) The number of tumors per mouse for the three different cohorts was assessed .

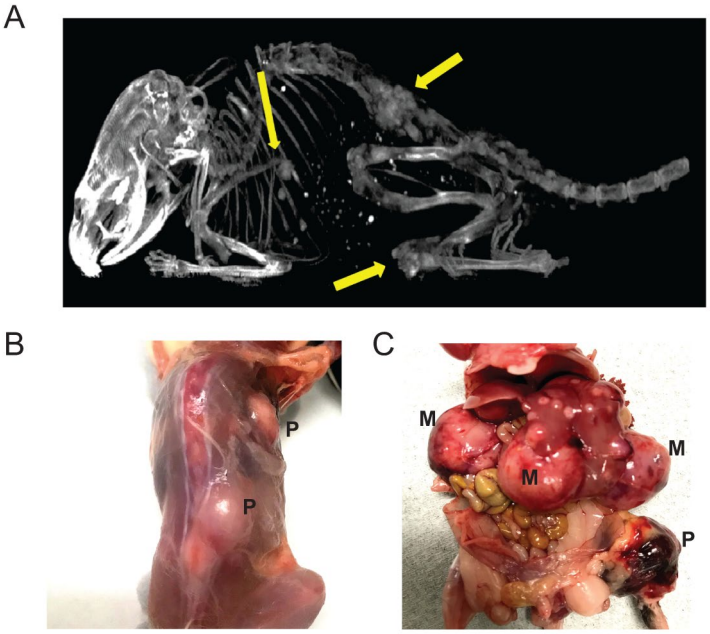

Figure 8. *In vivo* detection of osteosarcomas (A) MicroCT image of a mouse with several notalbe tumors indicated by yellow arrows. (B) Dorsal view of a mouse necropsy showing a primary tumor (P) on the ribs and lower lumbar region (C) Ventral view of a mouse necropsy showing a primary tumor on the left hindlimb and several metastatic tumors in the liver (M).

Poster #150 3463551

EFFICACY AND SAFETY OF TAZEMETOSTAT IN PATIENTS WITH INI1/SMARCB1- OR BRG1/SMARCA4-NEGATIVE TUMORS, OR RELAPSED/REFRACTORY SYNOVIAL SARCOMA

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Objective: Loss of inhibitor of integrase 1 (INI1), a member of the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling (CR) complex, allows enhancer of zeste homologue 2 (EZH2) to repress cell differentiation and promote tumorigenesis. NCT02601950 is a basket study designed to assess the efficacy and safety of tazemetostat, a first-in-class EZH2 inhibitor, in tumors lacking expression of INI1 (SMARCB1) or BRG1 (SMARCA4), harbor oncogenic activation of EZH2, or synovial sarcoma. Tazemetostat is FDA-approved for patients older than 16 years of age with inoperable metastatic or locally advanced epithelioid sarcoma (ES), and for adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies or for patients who have no satisfactory alternative treatment options. Here we report the efficacy and safety of tazemetostat in patients with solid tumors other than ES, including those with SWI/SNF inactivation, EZH2 gain-of-function, or synovial sarcoma.

Methods: This open-label, multicenter, phase 2 basket study evaluated efficacy and safety of tazemetostat (800 mg orally, twice daily) in multiple patient cohorts between December 2015 and April 2020. Here we report results in patients with rhabdoid tumors (Cohort 1); synovial sarcoma (Cohort 2); solid tumors lacking expression of INI1 or BRG1 or with EZH2 gain-of-function mutation (Cohort 3); and renal medullary carcinoma (Cohort 4). Patients with INI1-negative chordomas (Cohort 7) are currently enrolling in the study. Tumor response was assessed per RANO criteria for primary brain tumors or RECIST 1.1 criteria for all other solid tumors. The primary endpoints of the study were objective response rate (ORR; Cohorts 1, 3, and 4) and progression-free survival (PFS) at 16 weeks (Cohort 2). Secondary endpoints included duration of response (DOR, defined as the time from the first objective response to disease progression or death from any cause) and safety.

Results: 111 patients were enrolled and treated across Cohorts 1–4 (Table). ORR was 9% for Cohort 1 (3/32 patients) and Cohort 3 (3/32 patients). Median DOR was 6.7 and 18.4 months for Cohort 1 and Cohort 3, respectively. There were no objective responses in patients with synovial sarcoma (Cohort 2) and renal medullary carcinoma (Cohort 4). The median PFS was 1.8, 1.8, 3.6, and 1.7 months and estimated PFS at 16 weeks was 28.2%, 19.8%, 42.0%, and 23.1% in Cohorts 1, 2, 3, and 4, respectively. Treatment-emergent adverse events (TEAEs) were generally similar across cohorts and were reported in 105 (95%) patients; 56 (50%) had grade ≥3 TEAEs and 47 (42%) had serious TEAEs. Sixty-four (58%) patients had treatment-related AEs, 11 (10%) had grade ≥3 treatment-related AEs, and 5 (5%) had serious treatment-related AEs. The most common (≥20%) TEAEs in the total subset of patients were dyspnea (29%), nausea (29%), fatigue (28%), cancer pain (26%), vomiting (25%), and constipation (21%). Most common TEAEs for each cohort are shown in the table. TEAEs led to dose reduction, drug interruption, and drug discontinuation in 1%, 23%, and 4% of patients, respectively.

Conclusion: Tazemetostat induced durable objective responses in approximately 10% of patients with rhabdoid tumors or tumors lacking expression of INI1 or SMARCA4 (sinonasal tumor, small cell carcinoma of the ovary hypercalcemic type, and

spindle cell tumor). There were no objective responses seen in this single-arm study in synovial sarcoma or renal medullary carcinoma. Tazemetostat was generally well tolerated. These data support further investigation of tazemetostat in combination with other therapies in select histologies with SWI/SNF CR dysfunction.

Table.

	Rhabdoid tumors (Cohort 1) n=32	**Synovial sarcoma (Cohort 2) n=33**	**Other INI1-negative tumors (Cohort 3) n=32**	**Renal medullary carcinoma (Cohort 4) n=14**
Objective response rate, % (95% CI)	9 (2–25)	0 (0–11)	9 (2–25)	0 (0–23)
Best overall response, n (%)				
Complete response	1 (3)	0	0	0
Partial response	2 (6)	0	3 (9)	0
Stable disease	9 (28)	12 (36)	15 (47)	5 (36)
Progressive disease	16 (50)	21 (64)	10 (31)	6 (43)
Not evaluable	4 (13)	0	4 (13)	3 (21)
Duration of response, median months (range)	6.7 (5.5–7.4)	NE	18.4 (5.5–20.2+)	NE
Median PFS, months (range) 95% CI	1.8 (0.02+ to 14.8) 1.8–3.5	1.8 (0.5 to 12.6) 1.7–1.9	3.6 (0.3 to 33.1) 1.8–7.3	1.7 (0.02+ to 9.5) 1.4–3.8
Patients with TEAE, n (%)	29 (91)	31 (94)	32 (100)	13 (93)
TEAEs grade ≥3	21 (66)	15 (45)	13 (41)	7 (50)
Serious AEs	16 (50)	13 (39)	11 (34)	7 (50)
Patients with treatment-related AEs, n (%)	17 (53)	21 (64)	22 (69)	4 (29)
Most common TEAEs (all grades)[a], n (%)				
Dyspnea	7 (22)	11 (33)	7 (22)	7 (50)
Nausea	11 (34)	9 (27)	9 (28)	3 (21)
Fatigue	7 (22)	10 (30)	11 (34)	3 (21)
Cancer pain	10 (31)	9 (27)	8 (25)	2 (14)
Vomiting	13 (41)	1 (3)	9 (28)	5 (36)
Constipation	8 (25)	6 (18)	5 (16)	4 (29)
Cough	3 (9)	10 (30)	4 (13)	3 (21)
Decreased appetite	3 (9)	4 (12)	3 (9)	8 (57)
Anemia	5 (16)	4 (12)	4 (13)	4 (29)
Weight decreased	3 (9)	2 (6)	2 (6)	4 (29)
Dose reduction due to TEAE, n (%)	1 (3)	0	0	0
Drug interruption due to TEAE, n (%)	9 (28)	8 (24)	8 (25)	1 (7)
Drug discontinuation due to TEAE, n (%)	4 (13)	0	0	0

+, response ongoing.

[a]TEAEs appearing in ≥25% of patients in any cohort.

AEs, adverse events; CI, confidence interval; INI1, inhibitor of integrase 1; NE, not estimable; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Poster #151 3463563

BIOMARKERS FOR DELTAREX-G, THE SAFER CHECKPOINT INHIBITOR FOR SARCOMA: A SINGLE CENTER EXPERIENCE

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Objective: Metastatic cancer is associated with, hitherto, an invariably fatal outcome. DeltaRex-G (a tumor targeted gene vector encoding a CCNG1 inhibitor) has induced long-term (>12 years) survival in patients with metastatic sarcoma, lymphoma, and cancer of the pancreas and breast, with no dose-limiting toxicity or long-term adverse events. Molecular profiling of 2 long term cancer survivors revealed TP53, KRAS, PIK3CA and MAP kinase mutations. These oncogenic drivers fall along the CCNG1 pathway.

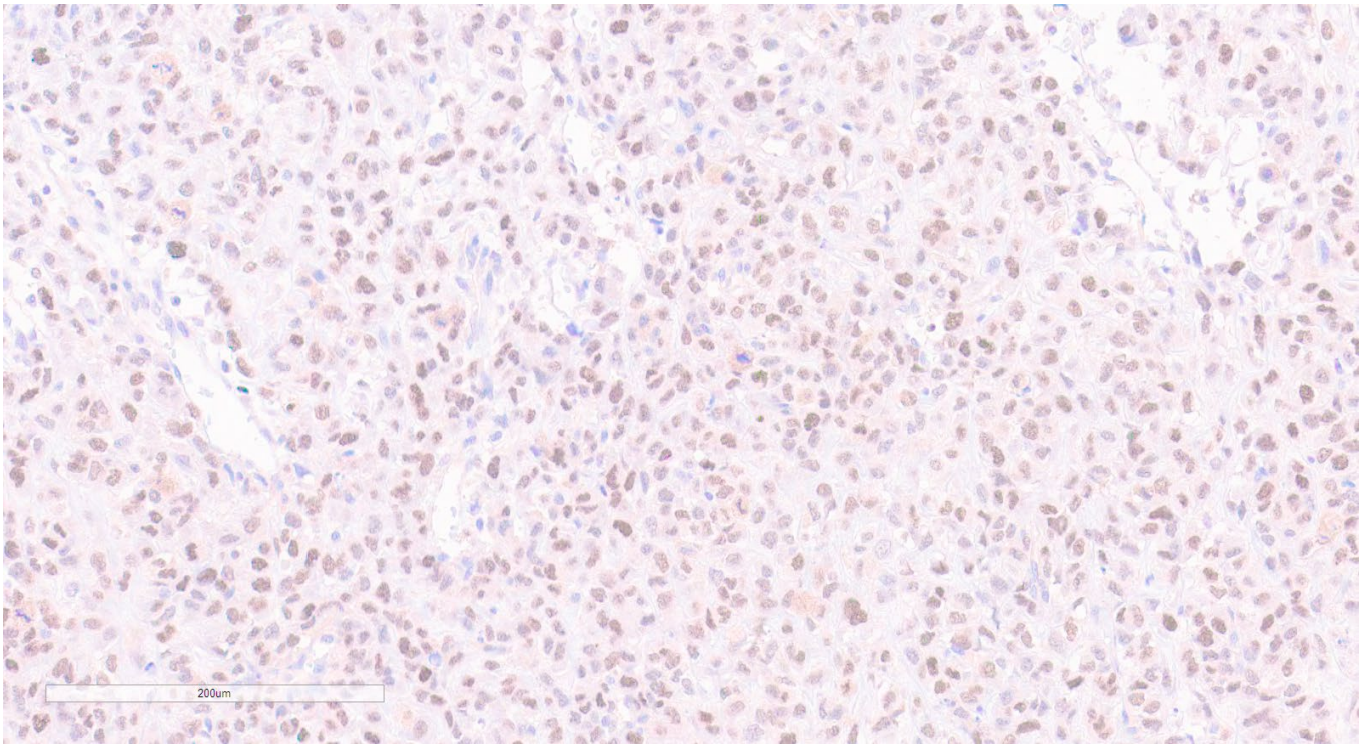
The objectives are:
1. To evaluate the frequency of genetic mutations along the CCNG1 pathway in patients with sarcoma; and
2. To identify patients who are likely to benefit most from DeltaRex-G tumor targeted gene therapy.

Methods: Four hundred fifty-one (451) patients were treated at the Cancer Center of Southern California/Sarcoma Oncology Center from October 2019 to April 2020. The archived tumors of one hundred fifty-seven (157) of these patients underwent molecular profiling. The data were reviewed for genetic mutations relevant to the CCNG1 pathway.

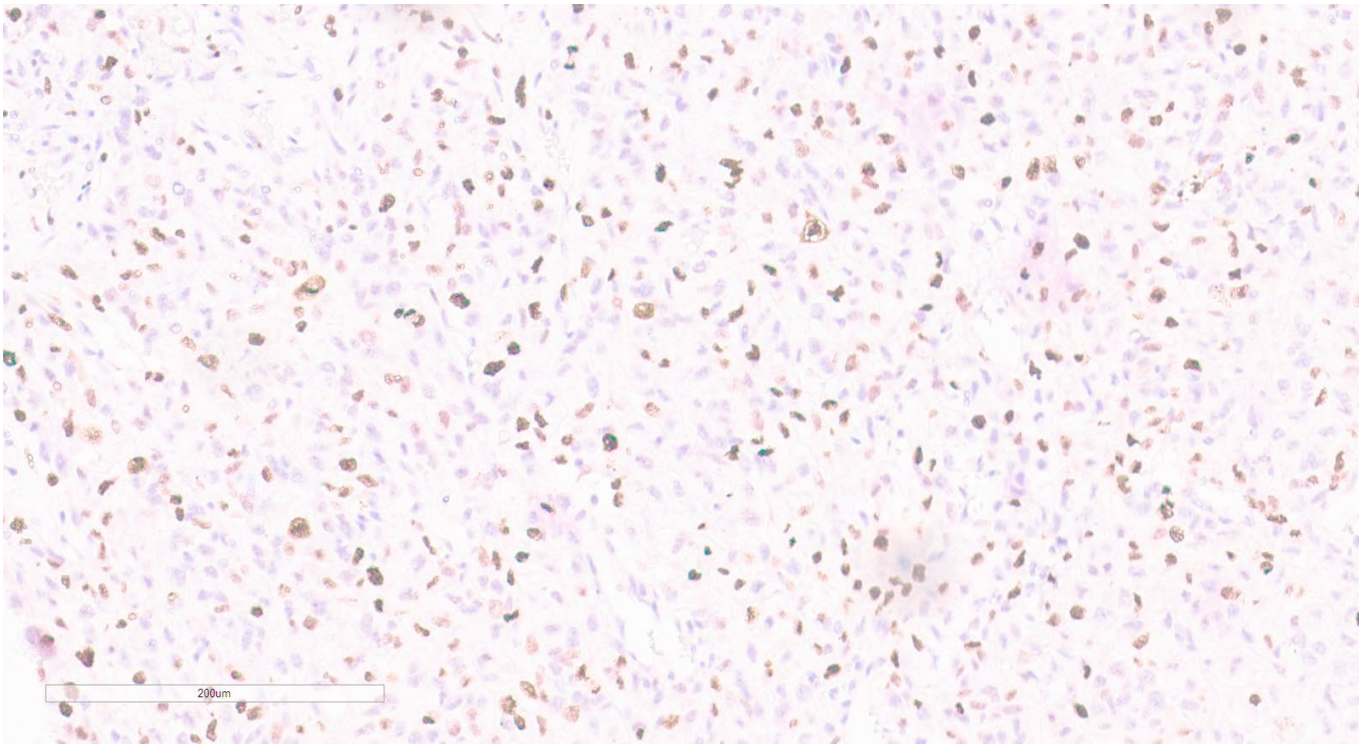
Results: The archived tumors of sixty-two of 157 (39.5%) patients with sarcoma had genetic mutations along the CCNG1 pathway. Fourteen out of 136 (9.3%) tested for the MDM2 gene amplification were positive; 2 out of 149 patients (1.3%) had MYC mutation with 1 patient having both MYC and MDM2 gene amplification; 36 out of 153 (23.5%) had TP53 mutation/loss. Three out of 155 (1.9%) tested for PIK3CA were positive. Ten out of 138 (6.8%) tested were positive for MAP3K1. The same percentage (6.8%) was found in those tested for MAP kinase. The tumors of 2 patients with leiomyosarcoma and osteosarcoma respectively showed enhanced expression of CCNG1.

Conclusion: Taken together, these data indicate that genetic mutations along the CCNG1 pathway are not uncommon in sarcoma. Further, these mutations could identify patients who are likely to benefit from DeltaRex-G therapy and may serve as biomarkers for long-term survival/cure, plausibly via eradication of the cancer stem cell as in patients with MYC mutation/amplification. Consistent with these findings, (1) The tumors of 2 long term cancer survivors showed TP53, KRAS, PIK3CA and MAP kinase mutations, and (2) Three of 54 (5.6%) of patients treated with DeltaRex-G in a US-based Phase 1 and Phase 2 study for metastatic chemotherapy-resistant sarcoma are long-term survivors (>12 years) with no further cancer therapy. A Phase 2 study using DeltaRex-G is planned to correlate treatment outcome parameters in patients with genetic mutations along the CCNG1 pathway.

Enhanced expression of CCNG1 (90%) in biopsied lung nodule of a patient with metastatic osteosarcoma.



Enhanced Ki-67 expression in biopsied lung nodule of the same patient with metastatic osteosarcoma.



Poster #152 3463590

TARGETING SPHINGOLIPID METABOLISM IN SYNOVIAL SARCOMA

Jared J. Barrott[1], *Sarah Luelling*[1], *Farjana Afrin*[1], *Adriene Pavek*[1], *Austen Kalivas*[1], *Srinath Pashikanti*[1]
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Objective: Synovial sarcoma is a rare soft-tissue sarcoma that affects adolescents and young adults. Overall survival for patients with synovial sarcoma is 39% at >15 years post diagnosis, and it is even more dismal for patients that present with metastatic disease at the time of diagnosis with a 5-year survival of 22%. There is a need to develop targeted therapies that can extend life for these young individuals with synovial sarcoma and improve their quality of life. The sphingolipid metabolism pathway is upregulated in synovial sarcoma, and it was our objective to determine if the pathway could be targeted to inhibit the function and growth of synovial sarcoma cells. Jaspine B is a natural product derived from marine sponges and targets sphingomyelin synthase 1 and 2. We applied jaspine B and chemical derivitives to synovial sarcoma models to better understand the potential for targeting this pathway in patients.

Methods: Jaspine B was synthesized in house and 4 analogues were synthesized as well. Established synovial sarcoma cell lines were treated with various concentrations of jaspine B and its analogues to determine potency using an MTT viability assay. Markers of apoptosis were detected via fluorescent activty of the enzymes Caspase 3 and 7. Sphingomyelinase activity was evaluated by enzyme assay test, and sphingosine kinase 1 protein expression was detected by immunoblotting. The metastatic mouse model for synovial sarcoma (SS18-SSX2^{OE};Pten$^{\Delta/\Delta}$) was used to determine if jaspine B could be effective against synovial sarcoma in vivo. Mice were dosed orally with 60 mg/kg of jaspine B 3X/week for 28 days or with control PEG400 solution. At the end of the 28 days, the control cohort crossed over and received dosing of jaspine B for additional 12 days.

Results: Jaspine B was synthesized as previously published by Dr. Pashikanti. Two analogues were generated by leaving the furan group intact and modifying the amine group at teh C-4 position on the furan ring. The other two analogues were generated by modifying the alkyl group at the C-2 position on the furan ring. Modifications to the amine group resulted in a complete loss in activity, whereas modifications to the alkyl group maintained relative potency but jaspine B was still the most potent. Upon investigating the mechanism of cell death, we observed active Caspase 3 and 7 after 24 hours of incubation at 0.5 uM. The application of jaspine B in synovial sarcoma cell lines resulted in the accumulation of ceramide, a pro-apoptotic metabolite in the sphingomyelin pathway. To investigate other arms of the pathway when sphingomyelin synthase is inhibited, we measured sphingomyelinase activity and observed a concomitant increase in enzymatic activity with increasing concentrations of jaspine B. Furthermore, sphingosine kinase 1 protein expression was elevated in synovial sarcoma cells after being treated with jaspine B.

A transgenic metastatic mouse model was administered jaspine B to determine if monotherapy could inhibit tumor growth. Mice were separated into treatment and control cohorts and dosed for 28 days. Treated mice demonstrated no tumor growth, while the control tumors doubled in tumor volume. Control mice then crossed over and began receiving oral treatments of jaspine B, which resulted in a modest decrease in tumor volume before the cancer grew over three times the initial volume and had to be euthanized by reaching endpoint criteria.

Conclusion: Targeted inhibition of sphingomyelin sythnase using jaspine B in synovial sarcoma resulted in increased ceramide accumulation, increased apoptotic signaling, and decreased tumor volume growth. While sphingomyelin synthase inhibitors proved effective, there is the potential to develop resistance through upregulation of other arms of the sphingolipid metabolism pathway to remove the toxic ceramide. This was evidenced by an initial response of large tumors to jaspine B, followed by persistent growth in the presence of sphingomyelin inhibition.

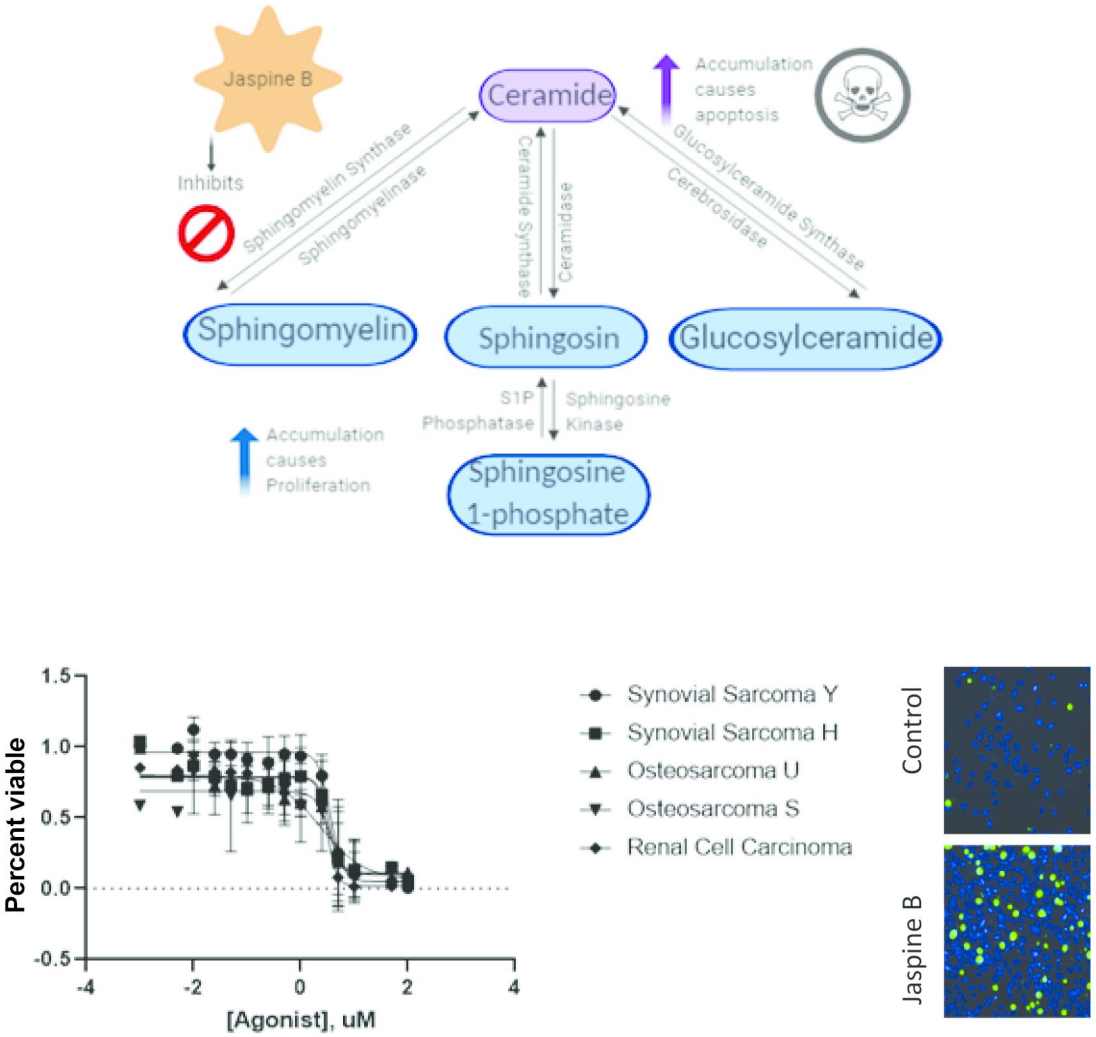

Figure 1. Jaspine B decreases cell viability and induces apoptosis in sarcoma cells. Left is a dose response curve demonstrating a low micromolar potency of jaspine B against 5 different cancer cell lines after 72 hours of treatment. The right fluorescent cell images demonstrate Caspase 3 and 7 activation in response to 0.5 uM Jaspine B after 24 hours in synovial sarcoma cells.

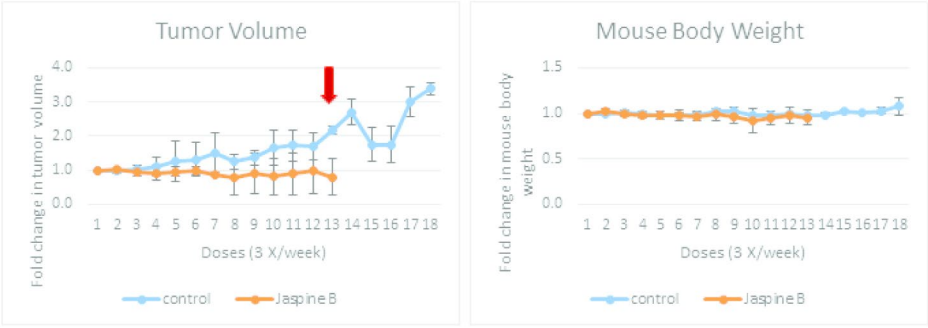

Figure 2. In vivo assessment of jaspine B in mice with synovial sarcoma. Mice on the control demonstrated an average 2-fold growth in tumor size, while the treated mice did not grow from their baseline measurements. Control mice crossed over to treatment on dose 13 (red arrow) and exhibited some response before growth of the tumor continued. Mouse body weight remained constant throughout the study for both control and treated mice.

Poster #153 3463619

30-YEAR FOLLOW-UP RESULTS OF 170 CEMENTED ENDOPROSTHETIC RECONSTRUCTIONS FOR TUMORS OF THE UPPER EXTREMITY

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Objective: Given the rarity of musculoskeletal tumors, particularly of the upper extremity, long-term survival data is heterogeneous and largely limited to small series. The objective of this study was to examine long-term outcomes of cemented stem endoprosthetic reconstruction for tumors of the upper extremity utilizing a large database with up to 30 years of follow-up.

Methods: 170 consecutive patients who underwent limb salvage surgery with endoprosthetic reconstruction for musculoskeletal tumors of the upper extremity between December 1980 and December 2019 were retrospectively reviewed. The average follow-up time of surviving patients was 8.1 years (range: 0.2 – 31.9y). All follow-up was performed at a single institution. Demographic, oncologic, procedural, and outcome data was collected and analyzed.

Results: 133 proximal humerus, 21 total humerus, and 16 distal humerus endoprostheses in 162 patients were included for analysis. 11 patients had expandable endoprostheses. The tumors were low grade (IA/IB) or benign in 31 patients, high grade (IIA/IIB) in 62, and metastatic carcinoma or stage III primary sarcoma in 69. Kaplan-Meier survivorship analysis revealed 95.0% disease-specific survival at 25 years for patients with low-grade or benign disease (Table 1, Figure 1). Only 1 patient with clear cell chondrosarcoma died of disease in the low grade/benign group. Disease-specific survival of patients with high-grade IIA/IIB disease was 53.1% at 30-years and only 7.7% at 20 years for patients with metastatic disease or stage III primary sarcoma. 44 of 69 (63.8%) of patients in this group died of disease. 30-year implant survival was 82.1% using revision of the stemmed components as the endpoint. Proximal humeral replacements demonstrated 96.7% survival at 25 years, while distal humeral replacements had the lowest survival at 40.1% at 20 years (Figure 2). Modular implants demonstrated better survival than custom-designed components, with a 25-year survival of 88.1% and 72.7%, respectively. 14 implants (8.2%) required revision, including 3 for aseptic loosening (1.8%), 6 for structural failure (3.5%), 4 for local recurrence (2.4%), and only 1 for infection (0.6%) (Table 2). Local recurrence occurred in 13 patients (7.6%), 9 of whom were treated with amputation (5.3%), the only amputations in the series. Survival of successful limb salvage was 88.9% at 30 years. For proximal humeral replacements, average shoulder range of motion was better following reverse total shoulder arthroplasty compared with hemiarthroplasty for both forward elevation and abduction (120.0° vs 36.7° [p=0.3] and 125.0° vs 35.7° [p=0.3], respectively).

Conclusion: The present study confirms the long-term durability of cemented endoprosthetic reconstructions of the upper extremity for musculoskeletal tumors, particularly of the proximal humerus.

Table 1: Upper Extremity Prosthesis Survival

	5-Year	10-Year	15-Year	20-Year	25-Year	30-Year
Implant Survival						
Custom (N=35)	90.8%	81.7%	72.7%	72.7%	72.7%	72.7%
Modular (N=135)	95.4%	92.8%	88.1%	88.1%	88.1%	-
Total Humerus (N=21)	88.0%	65.2%	65.2%	65.2%	65.2%	65.2%
Distal Humerus (N=16)	80.2%	80.2%	40.1%	40.1%	-	-
Proximal Humerus (N=133)	96.7%	96.7%	96.7%	96.7%	96.7%	-
Overall (N=170)	93.4%	89.0%	82.1%	82.1%	82.1%	82.1%
Patient Survival						
Low Grade IA/IB or Benign (N=32)	95.0%	95.0%	95.0%	95.0%	95.0%	-
High Grade IIA/IIB (N=61)	67.5%	60.3%	51.6%	51.6%	51.6%	51.6%
Stage III/Metastatic	29.5%	15.3%	7.7%	7.7%	-	-
Limb Salvage	92.5%	88.9%	88.9%	88.9%	88.9%	88.9%

Table 2: Modes of Failure Leading to Revision of Upper Extremity Endoprostheses

	Incidence of Implant Revision (N)			
Mode of Failure	Proximal Humerus (N=133)	Total Humerus (N=21)	Distal Humerus (N=16)	Total (N=170)
Soft Tissue Failure	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Aseptic Loosening	0.8% (1)	0.0% (0)	12.5% (2)	1.8% (3)
Structural Failure	0.8% (1)	14.3% (3)	12.5% (2)	3.5% (6)
Infection	0.8% (1)	0.0% (0)	0.0% (0)	0.6% (1)
Tumor Progression	1.5% (2)	9.5% (2)	0.0% (0)	2.4% (4)
Total	3.8% (5)	23.8% (5)	25.0% (4)	8.2% (14)

Figure 1: Disease-specific survival of patients with musculoskeletal tumors of the upper extremity following limb salvage surgery.

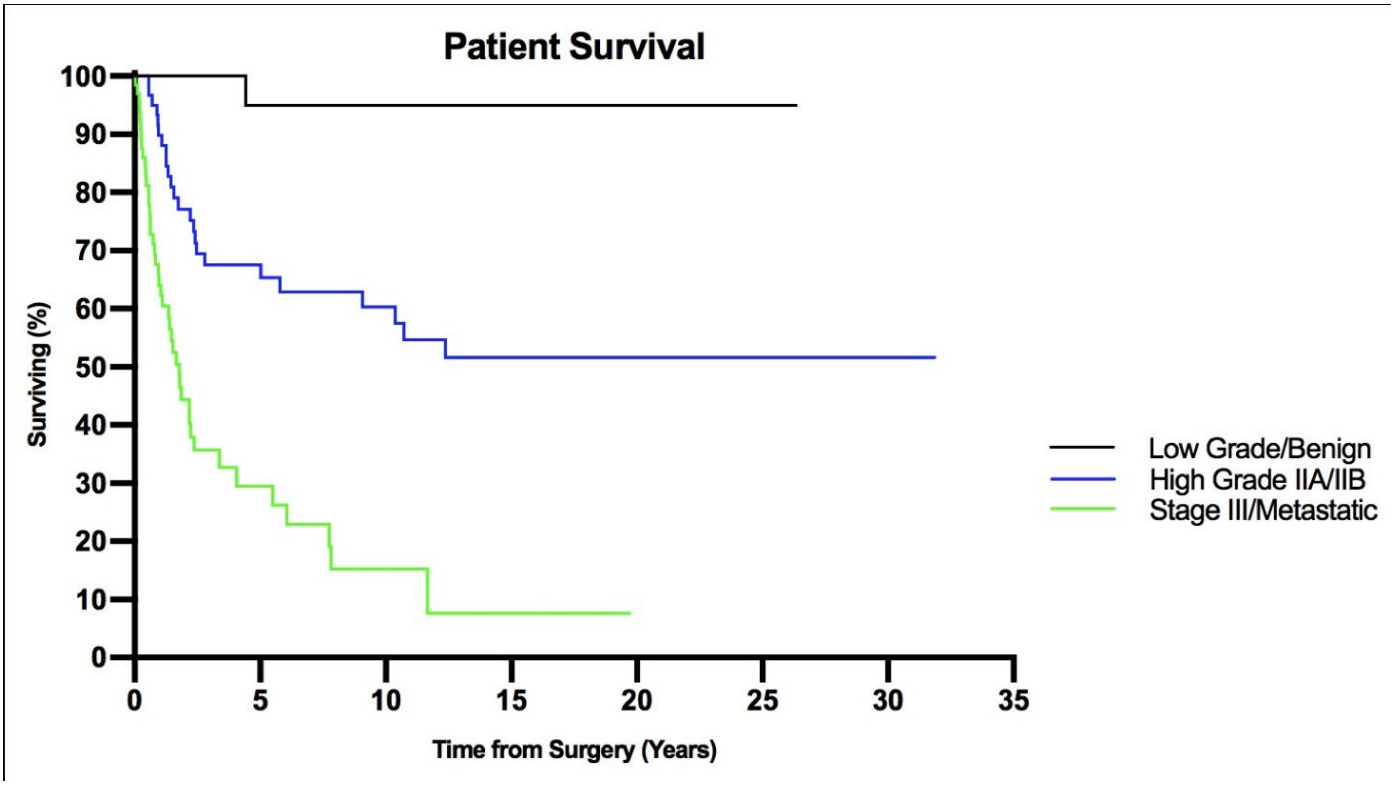
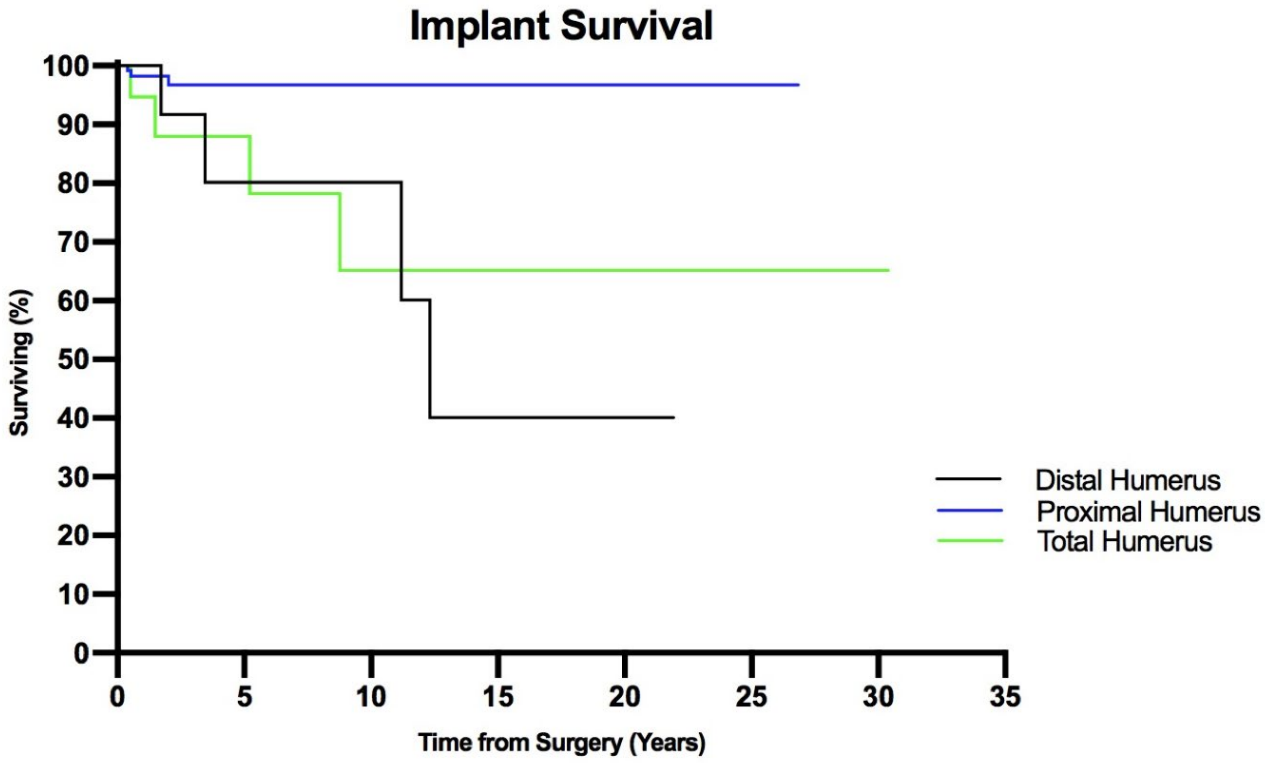


Figure 2: Implant survival to revision of stemmed components based on anatomic location of endoprosthetic reconstruction.



Poster #154 3463673

ACIDIC MICROENVIRONMENTS IN SOFT TISSUE SARCOMA PROMOTES FOXM1 EXPRESSION AND TUMORIGENESIS

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Objective: Acidic microenvironment is one of the characteristic features of malignant tumors. Accumulating evidence indicates that the acidic microenvironments critically influence malignant behaviors of cancer including proliferation, invasiveness, metastasis and chemoresistance. For sarcoma, it was reported that sarcomas were significantly more acidic than benign soft tissue tumors. However, the precise role of acidic microenvironment in sarcoma is still unclear. In the present study, we report on the relationship between the acidic environment and the transcription factor Forkhead Box M1 (FOXM1).

Methods: pH in the soft tissue tumor was measured immediately after resection using pH meter. The human dedifferentiated liposarcoma cell line SW872 were cultured in pH 7.4 and 6.4 DMEM with 10% fetal bovine serum. Microarray expression data was obtained from SW872 cells cultured at pH 7.4 and pH 6.4. Total RNA was extracted from the fresh frozen sample that obtained by open biopsy or resection. All experiments were conducted according to the ethical guidelines of the Institutional Review Boards and approved by the Ethics Committee of the Tokushima University.

Results: The average pH of resected tumor was 6.43±SD in malignant tumor (n=9), 7.03±SD in benign tumor (n=13), 7.19±SD in normal tissue (n=5) (Fig.1), suggesting that malignant tumor showed a significant acidic environment compared with benign tumor and normal tissue ($p<0.05$). SW872 liposarcoma cells treated with acidic medium (pH6.4) showed increased cell proliferation and invasion at 24 hours compared with cells at normal pH medium (Fig.2). Microarray analysis revealed some cancer related genes were elevated in acidic oH. Notably, expression of FOXM1 was remarkable among them. We examined the expression of FOXM1 in resected specimens of benign soft tissue tumor (n= 16) and malignant tumor (n= 11). As a result, FOXM1 was significantly highly expressed in malignant tumors (Fig.3). We examined expression of FOXM1 in SW872 cells cultured at pH6.4 and pH7.4 medium. Expression of FOXM1 was significantly elevated in SW872 cells cultured at pH 6.4 compared with cells at pH7.4 (Fig.4). Down-regulation of FOXM1 by thiostrepton reduced inhibits proliferation and migration ability of SW872 cells.

Conclusion: These data suggest that acidic microenvironment formed in malignant tumor activates FOXM1 and promotes sarcoma aggressiveness.

Poster #155 3463677

KAPOSI SARCOMA AFTER SOLID ORGAN TRANSPLANTATION, A SINGLE CENTRE EXPERIENCE

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Objective: Kaposi sarcoma (KS) is a multicentric vascular tumor associated with human herpesvirus type 8 (HHV-8). Solid organ transplantation recipients have an increased risk of this malignancy due to long term use of immunosuppressive agents. Most cases of post-transplant KS result from viral reactivation in immunocompromised patients. First line treatment for KS after organ transplantation is reducing immunosuppressive regimens, although resistant and advanced cases may need other treatment modalities including locorregional or systemic therapy with citotoxic agents. The aim of this series is to characterize the population of patients with KS post-transplant followed at an Oncology Department, regarding to clinical, pathological and demographic characteristics, treatment modalities required, outcomes and long-term follow up.

Methods: This is an observational, retrospective, single centre cohort study, which includes 20 patients with post-transplant KS followed at an Oncology Department until March 2020. Clinical and demographic features, treatment regimens and clinical outcomes were obtained from clinical files.

Results: In our sample, most patients were male (n=13, 65%) and had African origin (n=17, 85%). The median age at diagnosis was 48 years old (IQR 41-58). The primary presentation of KS was cutaneous lesions in 75% of patients (n=15), followed by visceral (n=4, 20%) and ganglionar disease (n=1, 5%). Most of our patients had received a kidney transplant (n=19, 95%), with only one patient (5%) being a cardiac transplant recipient. Median time from transplantation to diagnosis of KS was 11.5 months (IQR 6.25-19.5). The anatomopathological analysis reported positivity for HHV-8 infection in five patients (25%) and was non defining for the remaining 75% cases. Treatment included chemotherapy in 55% of patients (n=11), radiotherapy in 15% (n=3) and 30% (n=6) achieved remission of lesions with reduction of immunosuppressive agents alone. 65% (n=13) of our sample showed no progressive disease during time of follow-up, with a median follow-up of 77 months (IQR 11.7-121.9).

Conclusion: Post-transplant KS is strongly associated with immunosuppression and reactivation of HHV-8 virus. Most of our patients were from Sub-Saharan Africa, an endemic region for HHV-8 infection. However, only five patients were positive for this virus in biopsy specimens. This might be explained by the lack of HHV-8 immunostaining in older samples. Although most patients needed systemic treatment with chemotherapy, remission of lesions just by reducing immunosuppression was also observed in an important part of our sample. This is an unicentric retrospective analysis with a small sample of patients, thus its limitations should be noted.

Poster #156 3463723

NEOADJUVANT CHEMORADIOTHERAPY IN ADVANCED SOFT TISSUE SARCOMA: NASAR STUDY

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Objective: Patients with advanced soft tissue sarcomas (ASTS) have a poor prognosis. Several studies attempt to analyze the role of neoadjuvant chemotherapy (NACT) and radiotherapy (NART).

Methods: Prospective unicentric study in ASTS with neoadjuvant treatment based on epirubicin (60 mg/m2 day 1 and 2) and ifosfamide (1800 mg / m2 d1-5), every 3 weeks for 3 cycles, concurrently with NART (46-50 Gy) starting on day 22th. Adjuvant boost of NART may be administered after surgery. ASTS greater than 5 cm, high grade and deep localization, and those initially considered as unresectable were included. Patients were evaluated by radiology before and after of neoadjuvant treatment.

Results: From 2017 until now, fifteen patients with a median age of 43 years (range, 15-78) were enrolled in the study. 13 were men and 2 women.
9 of them were diagnosed of undifferentiated pleomorphic sarcoma, 2 angiosarcoma, 2 liposarcoma, 1 leiomyosarcoma amd one more of MPNST. 13 patients had histological grade 3 and the other grade 2. 12 tumours were located in the extremities, 2 in the scapula and the other in the pelvis. The median size was 10 cm (5- 20 cm). The median number of cycles was 3 (range, 2-5). The dose of RT was completed in all patients. 9 patients received RT boost after surgery. The clinical response was only obtained in 27% (4/15) of the patients. According to RECIST criteria, only 13,3% patients achieved a partial response (2/15), 67% a stabilization (10/15) and 20% a progression (3/15). According to PERCIST criteria, 73% patients achieved a partial response (8/11), 84% a stabilization (2/11) and only 9% a progression (1/11). The surgery was an en bloc resection, reaching complete resection in all patients.
The histological response was equal to or greater than 90% of necrosis in 67% (10/15), with 20% of the patients with a complete response (3/15) and 47% partial response (7/15).
The most frequent toxicity was delay in wound healing, requiring repair surgery in 2 patients, and 60% patients with skin toxicity grade 2.
With an average follow-up of 27 months (3-61 months), 8 patients remain without disease (53%) and 7 have had pulmonary relapses (47%). There was not local relapse in any of the patients.
Four deaths were registered due to metastatic tumor progression.

Conclusion: Neoadjuvant treatment with chemotherapy based on anthracyclines and ifosfamide concurrent with radiotherapy achieves a very high rate of pathological responses and no local relapse. Nonetheless, systemic relapses remain. PERCIST criteria have better correlation with necrosis than the RECIST criteria.

TABLE.

Histology	Inictial size (cm)	Clinical response	RECIST	PER CIST	Necrosis	Toxicity	Degree	Relapse	DFI (m)	Follow-up (m)	Exitus
UPS	13	YES	PR		100	Scar	2			49	NO
UPS	5	NO	SD		99	Skin	2			50	NO
UPS	13	NO	DP		90	Skin	2	Lung	7,3	22	YES
UPS	8,5	NO	SD		100	No		Lung	8,0	34	NO
UPS	15	NO	DP	PR	90	Skin	2	Lung	7,9	32	YES
UPS	6,6	YES	SD	PR	99	Scar	3			29	NO
UPS	6,3	NO	DP	SD	60	Scar	3	Lung	8,4	16	YES
MPNST	10	NO	SD	SD	70	Skin	2	Lung	8,2	23	YES
AGS	20	NO	SD	PR	100	Skin	2			16	NO
UPS	10	NO	SD	PR	99	Skin	2			13	NO
LPS	18	YES	SD	PR	95	Skin	2	Lung	8,3	12	NO
LMS	8,5	NO	PR	PR	70	Skin	1			10	NO
AGS	8	NO	SD	PD	10	Skin	2			6	NO
UPS	7	YES	SD	PR	95	Skin	2			4	NO
LPS	16	NO	SD	PR	10	Scar	2	Lung	15	28	NO

UPS = undifferentiated pleomorphic sarcoma; MPNST=Malingnant peripheral nerve sheath tumor; AGS = angiosarcomas; LPS=liposarcoma; LMS=leiomyosarcoma; DFI = disease free interval; PR= partial response; SD= stabilization disease; DP= disease progression.

Poster #157 3463757

GENOMIC LANDSCAPE OF METASTATIC SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcomas (STS) constitute a group of rare and heterogeneous tumors of mesenchymal origin. STS consist of over 50 different subtypes, with each subtype harboring distinct pathological features and clinical behavior. Despite the heterogeneity, almost all patients with metastatic STS (mSTS) are treated similarly with doxorubicin-based regimens as first-line treatment. Although multiple lines of systemic treatment are currently available, the prognosis of mSTS remains poor, with a median overall survival of 12-18 months. More insight into the biology of mSTS is needed to reveal clinically relevant and targetable molecular aberrations and to improve individual patient management. Here we employed whole genome sequencing (WGS) to map the genomic landscape of mSTS revealing novel genomic aberrations and actionable targets.

Methods: A total of 122 patients with mSTS were selected from the CPCT-02 study (NTC01855477) from the Center of Personalized Cancer Treatment. Fifteen hospitals across the Netherlands participated in this study. Core needle biopsies were obtained from the metastatic lesions and frozen in liquid nitrogen. In parallel peripheral blood was collected in CellSave or Streck tubes. DNA was isolated from biopsies and blood using an automatic set-up. A total of 50 – 200 ng of DNA was used as input for TruSeq Nano LT library preparation (Illumina). Barcoded libraries were sequenced as pools on HiSeq X and Novaseq 6000 sequencing platforms (Illumina) at the Hartwig Medical Foundation. Alignment and variant calling were carried out according to standard procedures. Germline variants in the blood sample were called with GATK Haplotype Caller v3.8 and consequently filtered in the matched tumor sample. Copy number variation, estimation of tumor mutational burden, mutational signature analysis and driver gene selection were carried out using state-of-the-art algorithms. To inventory potentially actionable targets, the precision oncology knowledge database OncoKB was used.

Results: Out of the 122 patients included, most biopsies were of metastatic GIST (n=40), leiomyosarcoma (n=28) and liposarcoma (n=10). The biopsies were most frequently taken from the abdomen/intra-abdominal cavity (n=40), liver (n=20), trunk (n=15) and the lungs (n=12). The median tumor purity of the biopsies was 72.2% (IQR 57.3 – 89.0). The biopsies had a median sequencing coverage of 103 (IQR 94-111) while the matched peripheral blood samples were sequenced at a median read coverage of 38 (IQR 34-42). In all mSTS biopsies, a median of 4007 single nucleotide variants (IQR 2,719-7,025), 415 insertions and deletions (IQR 300-581), 26 multiple nucleotide variants (IQR 16-46) and 71.5 structural variants (IQR 28-210) were observed. The median genome-wide tumor mutational burden was 1.57 mutations per megabase (IQR 1.08-2.65). Most tumors had diploid status, some a polyploid status and exceptionally a haploid status. The presence of kataegis and chromothripsis loci as well as fusion genes were identified. For the total cohort, >100 driver genes could be detected. The top 5 consisted of *KIT* (n=37, 30%), *RB1* (n=34, 28%), *TP53* (n=32, 26%), *CDKN2A* (n=28, 23%) and *DMD* (n=16, 13%). Importantly the top driver genes differed across the different STS subtypes. All of the 30 best known mutational signatures were represented in mSTS although in most of the tumor samples a considerable part of the genomic alterations could not be linked to a signature and the etiology remained unknown. In the whole group of mSTS at least one actionable target was detected in 66 samples (54%) for which an FDA approved or investigational agent is available.

Conclusion: To the best of our knowledge, this is the largest series with WGS data from metastatic STS lesions. This WGS analyses of mSTS gives important insights into the biology of these tumors and shows that sequencing efforts can serve as a tool to identify clinically relevant and targetable molecular alterations in individual patients.

Poster #158 3463788

IDENTIFICATION AND AUTHENTICATION OF A NOVEL "FET/ETS" FUSION ONCOPROTEIN IN EWING SARCOMA

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Objective: Development of more efficacious treatments for patients with Ewing sarcoma requires both an accurate diagnosis of the disease, and a better understanding of the molecular mechanisms of Ewing sarcoma development. All cases of Ewing sarcoma are associated with specific chromosomal translocations that encode "FET/ETS" fusion oncoproteins, most commonly EWS/FLI. To date, there have been seven chromosomal translocations associated with Ewing sarcoma. At the same time, rare cases exist in which Ewing-specific diagnostics fail to identify a known translocation. We now describe and functionally-characterize an eighth chromosomal translocation (the first identified in over ten years): a novel fusion of FUS and ETV4. We also validate FUS/ETV4 as a bona fide Ewing sarcoma translocation oncoprotein. We propose that FUS/ETV4 must be considered a bona fide FET/ETS fusion that mediates the development of Ewing sarcoma in rare cases.

Methods: We saw a 4-week old neonate with a left posterior mediastinal mass. The mass occupied a significant portion of the left thoracic cavity and had extensive intraspinal extension from T3 to T8. Clinical work-up revealed no evidence of metastatic disease. Open biopsy and thoracic laminoplasty were performed. The pathology of the biopsy specimens revealed classic Ewing sarcoma with sheets of small round blue-staining cells with no evidence of differentiation. The tumor was CD99-positive in a diffuse membranous staining pattern. EWSR1 rearrangement was not detected, so FUS break-apart FISH was performed and identified a rearrangement at 16p11.2. Molecular genetic testing revealed a translocation between the FUS locus on chromosome 16p11.2 and the ETV4 locus on chromosome 17q21. We then cloned the FUS/ETV4 fusion and compared it to other FET/ETS translocations in a series of functional assays, including in vitro transcriptional activation assays and in vivo assays that allowed us to determine the oncogenic transformation potential, genomic localization patterns, and transcriptomic profiles associated with each fusion protein.

Results: This represents the first reported case of a FUS/ETV4 translocation in Ewing sarcoma. Genomic sequencing revealed the fusion occurs between exon 10 of FUS and exon 9 of ETV4, effectively joining the intrinsically-disordered transcriptional regulatory of FUS to the DNA-binding domain of ETV4. Molecular analysis revealed FUS/ETV4 was able to regulate transcriptional activation via GGAA-repetitive microsatellites in a luciferase reporter assay in a similar manner to other Ewing sarcoma fusions. Genome-wide studies revealed that FUS/ETV4 binds and regulates similar gene targets as other Ewing sarcoma fusions with some apparent differences in affinity and gene regulatory ability.

Conclusion: Taken together, these data authenticate FUS/ETV4 as the eighth FET/ETS fusion associated with Ewing sarcoma, and the first discovered in the last decade. These data have important implications for the diagnosis and treatment of Ewing sarcoma, particularly for the "EWS-translocation negative" group, for the design of highly-focused molecular diagnostics, and future therapeutic approaches for this disease.

Poster #159 3463800

CUTANEOUS ANGIOSARCOMA: CLINICAL AND MOLECULAR PROFILE AND IMMUNOTHERAPY IN A CASE SERIES

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Objective: cutaneous angiosarcoma is an aggressive subtype of soft tissue sarcoma arising from vascular endothelial cells, with poor prognosis and limited treatment options. (1) Standard treatment is wide local excision followed by radiation, but recurrence and metastatic disease are common. (1-3) Taxanes and anthracyclines have efficacy for metastatic disease but lack durability, and prognosis remains poor. (3) Thus, there is great interest in describing the molecular genetic profile of these tumors to identify better treatment options. (1) Checkpoint inhibitors have demonstrated impressive responses in some series, but data remain mixed, and no large scale trials have been reported to date. (4,5) Recently, a larger series of angiosarcoma molecular profiles reported commonly mutated genes including TP53 (29%), ARID1A (17%), POT1 (16%) and immunotherapy markers (36%). (6) To our knowledge, no studies have described both molecular profile and treatment response. We report a case series of 10 consecutive patients at our institution with molecular profiling in addition to clinical course and treatment response.

Methods: we performed retrospective chart review on consecutive angiosarcoma patients identified in our dermatology and sarcoma oncology clinics. We extracted demographic data, treatment received, PD-L1 molecular characterization, strata tumor genomic testing and treatment response. We calculated proportions but did not perform statistical analysis given the small sample size.

Results: we identified 10 patients with cutaneous angiosarcoma at our institution since 2017; 75 years old on average, 50% female and 90% caucasian. 70% Of patients had high pdl1 expression by ihc. Patients received paclitaxel (5), liposomal doxorubicin (1) and pembrolizumab (5). Two patients did not have recurrent or metastatic disease. One patient was referred for clinical trial at another institution, but records were not available. One patient with recurrent disease received preoperative pembrolizumab, three received it in the second line setting after progression with taxanes, and one received it upon first recurrence. Response to systemic therapy was varied. For patients treated with taxanes, one is off therapy due to a complete response from paclitaxel, another had 2 years of disease control prior to recurrence, while two patients progressed within months of initiation. In patients treated with pembrolizumab, one demonstrated disease progression despite preoperative therapy but has no evidence of disease after excision and radiation. One patient had progression within 3 months despite high pd-l1 expression. Another patient had an excellent response after only 3 months of therapy and has no evidence of disease, although treatment was held due to immune related toxicity. Two other patients had excellent responses, which have been durable for 8 and 25 months respectively. Strata NGS testing demonstrated high pd-l1 (3), mutations in TP53 (2), HRAS (1), BRAF (1), NRAS (1), CDKN2A deep deletion (1), no alterations (2) and pending (3).

Conclusion: our case series highlights the variable clinical course of cutaneous angiosarcoma, sometimes curable with excision and radiation, but often recurrent and metastatic. Genetic makeup of these tumors will be reported in full, including TP53 mutation rate and proportion of high PDL1 expression, and clinically annotated. Standard of care therapies such as taxanes and anthracyclines have limited benefit, as the majority of patients in our series progressed on these. Preliminary results suggest a notable proportion with high PD-L1 expression, mutations in the MAPK pathway, and TP53 mutations. Pembrolizumab is promising, but several patients had rapid disease progression despite high PDL1 expression, suggesting the role for combination immunotherapy. Larger scale studies, such as the upcoming alliance A091902 trial, are needed to better characterize the molecular profile and improve treatment response in this still lethal disease.

Poster #160 3463802

FEWER THAN TWO PULMONARY MICRONODULES IDENTIFIED ON PRESENTATION IN PATIENTS WITH OSTEOSARCOMA HAVE NO EFFECT ON 5 YEAR OVERALL SURVIVAL

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Objective: The wide spread adoption of high resolution CT scans in the last 25 years have revealed pulmonary micronodules not previously seen and surgical recommendations have not recently changed to reflect this reality, therefore our objective is to study the relationship between number of lung nodules discovered on CT at the time of diagnosis of osteosarcoma (OST) and 5 year overall survival to aid in the revision of surgical guidelines.

Methods: We retrospectively collected data on all newly diagnosed OST patients, age less than 50, treated at Rush University Hospital over 25 years from 1995-2020 who had an initial CT chest within 1 month of diagnosis. Lesions were counted as micronodules if they were not explicitly defined as benign, if they were surrounded by lung parenchyma, and if they were ≤ 8 mm. Size, location of nodules, and if they were resected, was recorded. Additionally, dates of last known alive and dates of death were recorded. Kaplan Meier curves, Tarone-Ware tests, t tests, and 1 and 2 way ANOVAS, were run using RStudio.

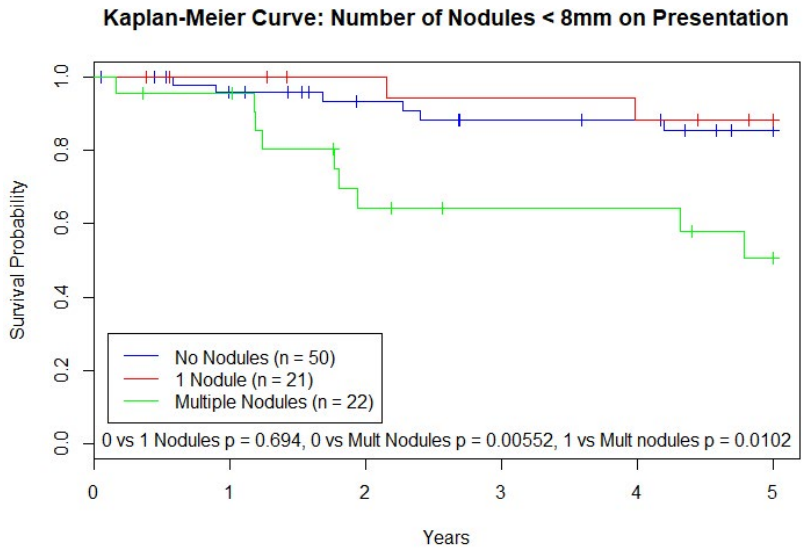
Results: Over 25 years, there were 93 patients (mean age = 21, range = 6-48, 40F, 53M) that fit our inclusion and exclusion criteria. Of the 67 patients who we had conformation at 5 years if they were alive or dead, 52 were still alive (78%). 43 patients had nodules on presentation and 50 did not. Only one patient had a lung surgery immediately after identifying nodules (6 nodules, largest 8 mm) on CT at presentation. On presentation, 21 patients had 1 nodule, 16 patients had 2 nodules, 6 had multiple nodules, and only the 0 and 2 nodules groups had statistically different 5 year survival rates ($p = 0.00883$, Table 1). Kaplan-Meier curve indicates a similar 5 year overall survival between patients with 0 and 1 nodule on presentation, but patient with 0 and 1 nodules both have a significantly longer 5 year overall survival than patients with multiple (≥2 nodules), (graph 1, $p = 0.006$, 0.01, respectively). Additionally, this relationship held true when only including patient with largest nodule < 4 mm ($p = 0.0118$, $p = 0.0111$, respectively). When patients with exactly 2 nodules were compared to patients with 0 and 1 nodule, the Kaplan-Meier curve indicated a lower 5 year survival for the 2 nodule group (graph 3). There were an additional 18 patients who we had conformation if they had a lung nodule at 1 year of diagnosis (n = 111, mean age = 21, 52F, 59M). Of the 81 patients who we had conformation at 5 years if they were alive or dead, 64 were still alive (79%). Kaplan-Meier curve comparing patients with micronodules within 1 year to patients with no micronodules within 1 year shows patient with nodules have a significantly lower 5 year overall survival (graph 4, $p = 0.0053$), a finding which was not seen when comparing patient with micronodules ≤ 8 mm to patients with no nodules on presentation (graph not shown, $p = 0.17$).

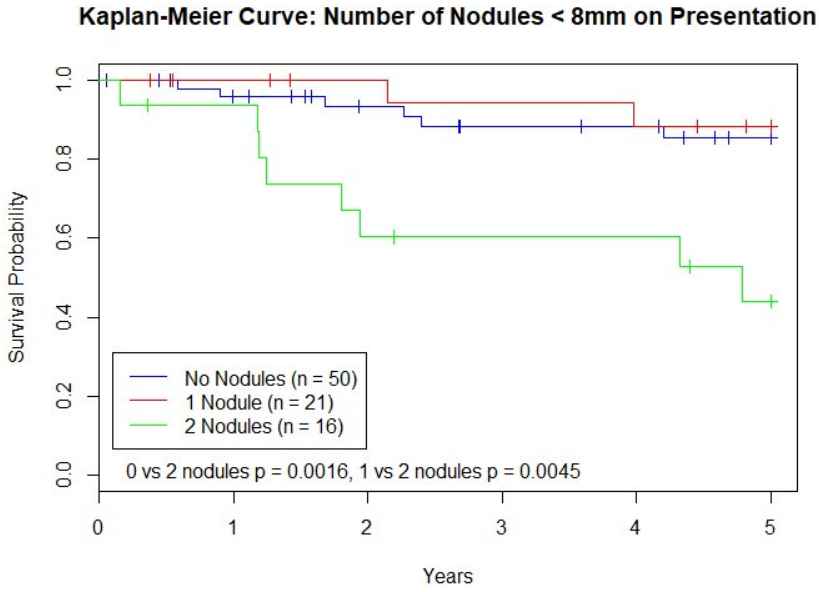
Conclusion: Our retrospective, single institution study of 111 patients showed a survival advantage for those who presented with 0 or 1 nodule compared to 2 nodules, both when including nodules ≤ 8 mm, and when including nodules < 4 mm, however, there was no difference in 5 year overall survival for patients with 1 nodule ≤8 mm compared to patients with no nodules. On presentation, there was no difference in 5 year overall survival between patients with no nodules or ≥1 nodule, however, at 1 year, patients with any number of lung nodules identified indicated a significantly lower 5 year overall survival. Standard practice has been to remove all visible nodules, however, these recommendations have existed for 25 years, before high resolution CT showed nodules less than 3 mm. Our data suggest surgery is not necessary for solitary micronodules ≤ 8 mm identified on presentation, but is necessary for micronodules seen 1 year after presentation.

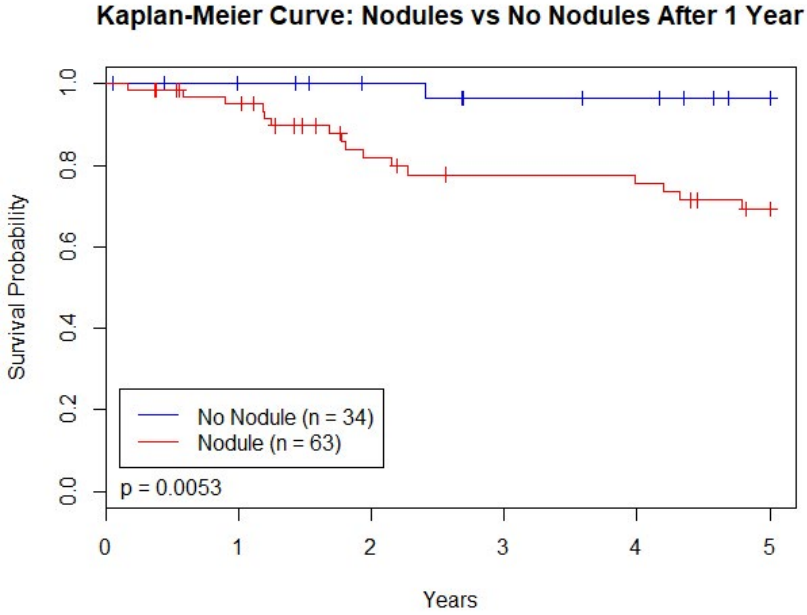
5 Year Death Rates

Number of Nodules ≤ 8 mm on Presentation	Total	Deaths	Percent Survival
0	49	9	82%
1	21	5	76%
2	16	9	44%
Multiple	6	1	83%

0 nodules vs 2 nodules $p = 0.008834$


Kaplan-Meier Curve: Number of Nodules < 8mm on Presentation
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
No Nodules (n = 50)
1 Nodule (n = 21)
Multiple Nodules (n = 22)
0 vs 1 Nodules p = 0.694, 0 vs Mult Nodules p = 0.00552, 1 vs Mult nodules p = 0.0102
0
1
2
3
4
5
Years


Kaplan-Meier Curve: Number of Nodules < 8mm on Presentation
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
No Nodules (n = 50)
1 Nodule (n = 21)
2 Nodules (n = 16)
0 vs 2 nodules p = 0.0016, 1 vs 2 nodules p = 0.0045
0
1
2
3
4
5
Years


Kaplan-Meier Curve: Nodules vs No Nodules After 1 Year
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
No Nodule (n = 34)
Nodule (n = 63)
p = 0.0053
0
1
2
3
4
5
Years

Poster #161 3463844

MALIC ENZYME 1 ABSENCE IN SYNOVIAL SARCOMA ALTERS GLUCOSE METABOLISM AND THE GLUTATHIONE-THIOREDOXIN AXIS

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Objective: Synovial Sarcoma (SS) is an aggressive malignancy and accounts for ~10% of all soft tissue sarcomas. In a metabolic screen we discovered that SS lacks expression of Malic Enzyme 1 (ME1). ME1 is a cytosolic producer of NADPH, a reducing equivalent used in antioxidant recycling and reductive biosynthesis. We hypothesized that ME1 absence in SS alters cell metabolism and redox homeostasis.

Methods: We analyzed a mRNA microarray of metabolic enzymes, and we confirmed the results with IHC. We performed western blot and qPCR analysis of ME1 expression using SS cell lines and tumor samples. A retroviral system was used to generate ME1 overexpressing cell lines from ME1 negative SS cell lines and a ME1 knockdown cell line. ME1(+) and ME1(-) cell lines were used in seahorse assays, cell death analyses, C_{13} glutamine tracing, and metabolomic analyses.

Results: The mRNA microarray showed reduced ME1 expression in SS. Western blot, qPCR, and IHC confirmed absence of ME1 expression in SS. Glycolytic rate assays and fuel flex assays revealed reduced glucose utilization in glycolysis and OxPhos in ME1(-)SS. Metabolomic data indicated increased levels of pentose phosphate pathway (PPP) intermediates in ME1(-)SS. Glucose withdrawal experiments demonstrated increased dependency on glucose for maintenance of NADPH levels in ME1(-)SS relative to ME1(+)SS. Cell death analysis showed increased sensitivity to DHEA in ME1(-)SS, suggesting dependence upon the PPP. Metabolomic data indicated reduced levels of GSH and U-C_{13}glutamine tracings demonstrated reduced incorporation of glutamine into GSH in ME1(-)SS, suggesting reduced synthesis of GSH. Cell death analysis showed reduced sensitivity to BSO inhibition of GSH synthesis in ME1(-)SS. Conversely, cell death analysis demonstrated significantly increased sensitivity to D9 inhibition of the thioredoxin system in ME1(-)SS.

Conclusion: We have shown that SS lacks expression of ME1. Functional characterization of ME1(-)SS demonstrated increased dependency upon the pentose phosphate pathway and a shift in dependency from the Glutathione system to Thioredoxin system. Understanding the metabolic consequences of ME1 absence in synovial sarcoma may aid in the development of targeted therapeutics.

Poster #162 3463876

PROXIMAL FEMORAL REPLACEMENT IN THE TREATMENT OF ONCOLOGIC DISORDERS OF THE PROXIMAL FEMUR: THE EXPERIENCE OF A SINGLE INSTITUTION

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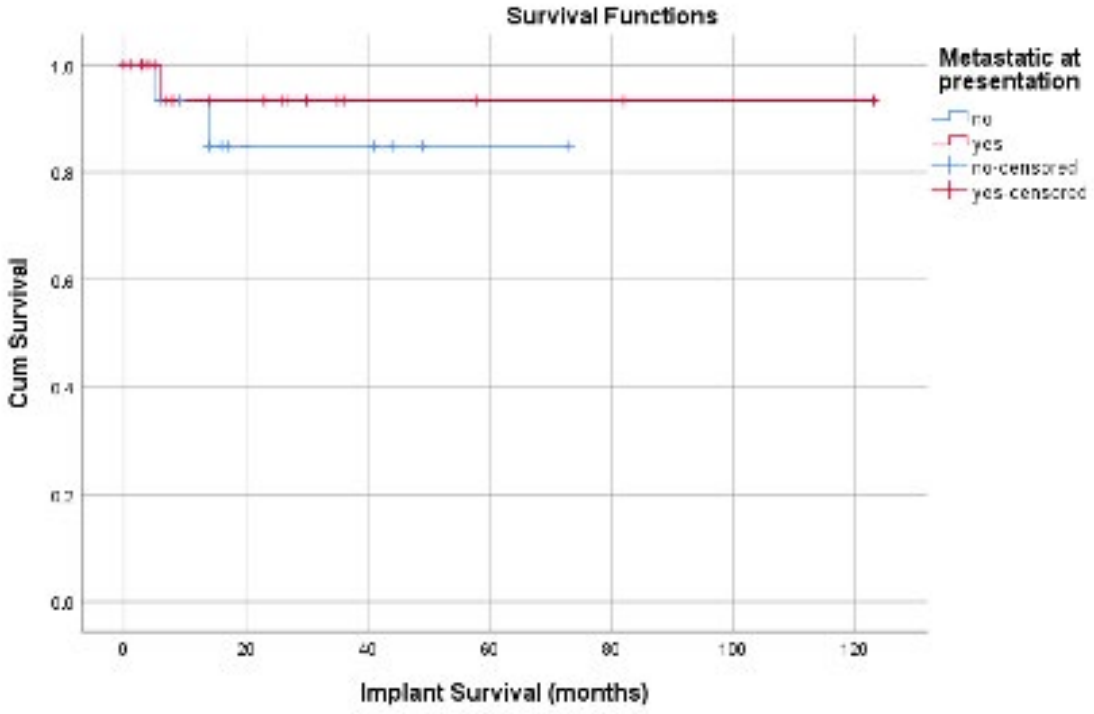
Objective: The proximal femur is a common site of benign tumors, primary malignancy, and bony metastases. For patients with destructive lesions of the proximal femur, surgical decision-making can be complex, as each reconstructive option has various risks and benefits. In cases of significant bony destruction, the best oncologic and functional option often may be proximal femoral replacement. In previous literature reports, modular oncology reconstructions have demonstrated significant rates of dislocation, infection, and stem loosening, as well as low rates of implant survivorship. As surgical techniques and implant design have improved over time, uncertainty still remains regarding the true rates of proximal femoral replacement survivorship and perioperative complications. This study sought to determine whether using modern surgical technique including implants and postoperative protocols could improve upon historical data. The aims of this study include: 1) an analysis of a high-volume, sarcoma institution's experience with proximal femoral replacement to assess implant longevity; and 2) an examination of the perioperative complication profile for resection of the proximal femur and reconstruction with an endoprosthesis, to assess the safety of its use in patients with solitary and metastatic tumors.

Methods: Following IRB approval, this retrospective study queried a prospectively maintained surgical database from 2005 to 2019 in order to identify patients with metastatic disease, primary tumors, and nononcologic conditions of the proximal femur treated with proximal femoral endoprosthesis. Medical records including preoperative and postoperative imaging were reviewed, and complications and implant survival were recorded.

Results: A total of 42 consecutive patients (43 arthroplasties) were recorded from 2005 to 2019, with 36 performed between 2014 and 2019. Sixteen females and 26 males with an average age (mean, IQR) of 60.93 (71-54) years comprised the study population. Predominant diagnoses were metastatic bone disease (n=20; 46.5%), chondrosarcoma (n=9; 20.9%), and osteosarcoma (n=4; 9.3%), and miscellaneous diagnoses included Ewing's sarcoma, soft tissue sarcoma, myxofibrosarcoma, and lymphoma. The average surgical duration (mean ± SD) was 175.6 ± 86.8 minutes. Thirty-six procedures were hemiarthroplasty, 4 were total hip standard bearing, and 2 were total hip dual mobility. The average intraoperative blood loss (mean ± SD) was 610.6 ± 406.5 mL, and the average length of hospitalization (mean, range) was 6.88 days (2-19). The overall perioperative complication rate (Clavien-Dindo Grading System) was 37% (acute kidney injury, Grade I = 2; urinary tract infection, deep venous thrombosis, Grade II = 1; atrial fibrillation, Grade II = 1; Grade II =1; blood transfusion, Grade II = 7; dislocation, Grade III = 3). Five-year estimated event-free implant survival probability was 0.9 for those with metastatic disease with an estimated mean survival (95% CI) of 115.2 (100.4-129.9) months, and 0.85 for those without metastatic disease, with an estimated mean survival of 63.5 (51.2-75.7) months (p=0.538). The rate of all-cause revision was 7.1% (n=3) at a mean (range) of 13.7 (1-32) months following surgery, either from dislocation (n=1), infected dislocation (n=1), or periprosthetic infection (n=1). The mortality rate was 2% within 60 days of surgery, and follow-up time (mean, range) defined as the last documented orthopedic or tumor-related encounter was 9.95 (0-61) months.

Conclusion: Proximal femoral endoprostheses offer a safe and reliable treatment option for patients with extensive metastatic disease or solitary tumors of the proximal femur. Despite a homogenously distributed sample size due to data lost in medical record transition, we believe our low modern rates of complication and revision with high, event-free midterm survival are due to a combination of improved surgical technique, implant innovation, and postoperative protocol adherence including use of a brace.

Figure 1. Cumulative implant survivorship. Kaplan and Meier event-free implant-related survivorship estimates for PFR cases presenting with and without metastatic bone disease as measured from time of modular endoprosthesis placement to an end point of revision, amputation, or last documented time alive in medical record with no complication including revision having occurred. PFR, proximal femoral replacement (p=.538).



Poster #163 3463885

DISTAL FEMORAL REPLACEMENT FOR TREATMENT OF ONCOLOGIC DISORDERS OF THE LOWER EXTREMITY: THE EXPERIENCE OF A SINGLE INSTITUTION

Charles Gusho[1], *Bishir Clayton*[1], *Joshua Greenspoon*[1], *Jonathan Bauer*[1], *Matthew Colman*[1], *Steven Gitelis*[1], *Alan Blank*[1]
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Objective: The distal femur is the most common site for primary tumors of the bone. While intralesional procedures such as curettage are performed in cases of benign and metastatic pathology, more aggressive tumors and sarcoma are treated with wide resection and reconstruction. Various modalities of limb salvage include modular oncology and endoprosthetic replacement, allograft reconstruction, or rotationplasty. Modular oncology reconstruction, however, is the most commonly performed limb salvage procedure. Though initially reliable, distal femoral endoprostheses carry a high risk of long-term infection, mechanical breakage, and aseptic loosening as reported in preexisting literature. Some series describe 10 and 20-year survival estimates nearing only 50%. However, despite device-related complications, modular endoprosthetic reconstruction is still a common treatment for patients requiring limb salvage. This study sought to determine whether modern surgical techniques including implants portend an improved device-related survival and overall complication profile for the treatment of distal femoral lesions. The aims of this study include: 1) analysis of a high-volume, single institutional experience with distal femoral replacement to assess implant longevity, functional outcomes, and patient satisfaction; and 2) examination of the perioperative complication profile following resection of the distal femur and reconstruction with an endoprosthesis, to assess the safety of its use in patients with solitary and metastatic tumors.

Methods: Following IRB approval, this retrospective study queried a prospectively maintained surgical database to identify patients with metastatic disease, primary tumors, and nononcologic conditions of the distal femur treated with distal femoral endoprosthetic reconstruction with a modular endoprosthesis. Medical records including preoperative and postoperative imaging were reviewed, and complications and implant survival were recorded.

Results: From 2005 to 2019, 102 patients (52.9% female) of an average age (mean, IQR) of 36 (58-16) years at surgery and a mean follow-up (SD) of 64.65 ± 81.81 months were reviewed. The predominant diagnoses were osteosarcoma (n=60; 58.8%), metastatic lesions (n=13; 12.7%) and giant cell tumors (n=7; 6.9%). Femoral stem fixation was achieved with cement in 79 (77.5%) cases, press-fit in 16 (15.7%) cases, and with a compress system in 2 (2%) cases. The average surgical duration (mean ± SD) was 160.75 ± 68.63 minutes, and the average length of hospitalization (mean, range) was 5.09 (2-19) days. The overall perioperative complication rate (Clavien-Dindo Grading System) was 26.5% (neuropraxia, Grade I = 3; blood transfusion, Grade II = 17; deep venous thrombosis, Grade IV = 1; and pancreatitis, Grade IVa =1. Five and 10-year event-free implant-related survival probabilities from cases performed before 2010 as estimated by Kaplan and Meier were 0.7 and 0.5, respectively, with an estimated mean survival time (95% CI) of 125.3 (90-159) months (Figure 1). For cases after 2010, the Kaplan and Meier 5-year estimated event-free implant survival probability was 0.9 with a mean estimated survival time (95% CI) of 90.8 (73-108) months (Figure 2). All-cause revision for the entire study period was 33% (n=34) as a result of aseptic loosening (n=10), infection (n=8), hardware complications including fracture and component failure (n=11), and patellar-specific revision (n=5).

Conclusion: Use of a modular endoprosthesis for distal femoral reconstruction in oncologic conditions is a durable and safe short to intermediate-term (<10 years) option for patients who require limb salvage. We believe innovation both in implant design and surgical technique over time are the primary contributing factors to modern increased event-free implant-related survival. However, our all-cause revision rate of 33% is a key counseling consideration and patients should be advised of the high likelihood for future surgery and the associated complications.

Figure 1. Cumulative implant survival before 2010: Kaplan and Meier device-related survivorship estimates for all cases performed before 2010, as measured from time of modular endoprosthesis placement to an end point of revision, amputation, or last documented time alive in medical record with no complication including revision having occurred.

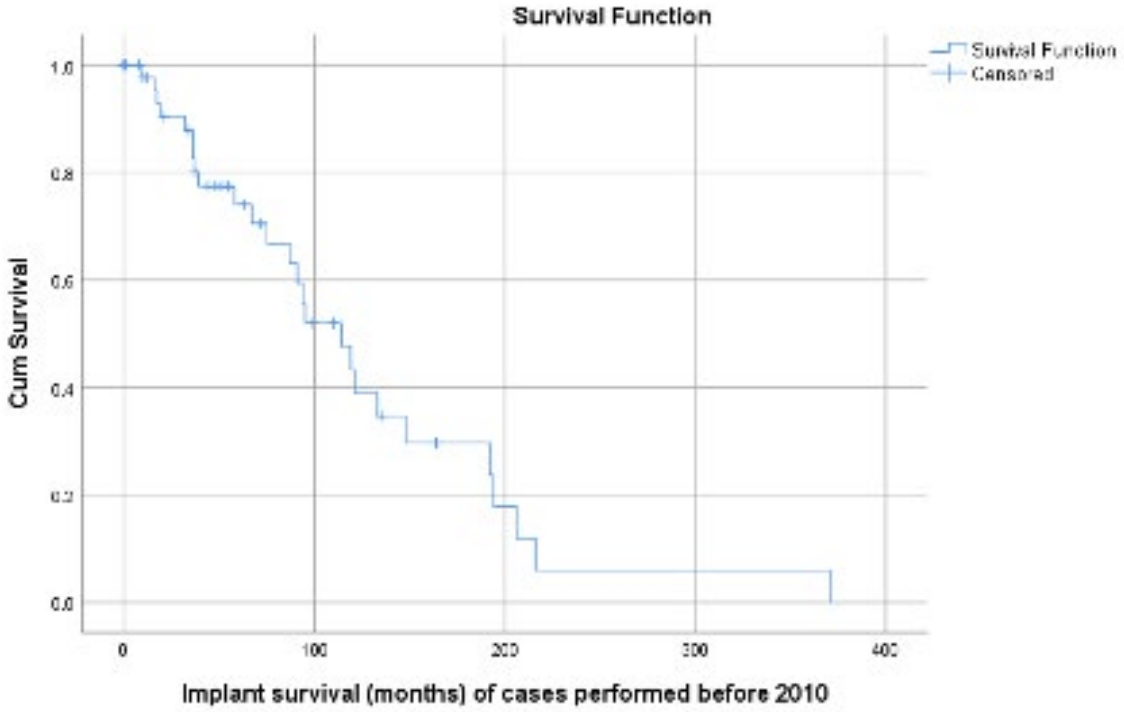
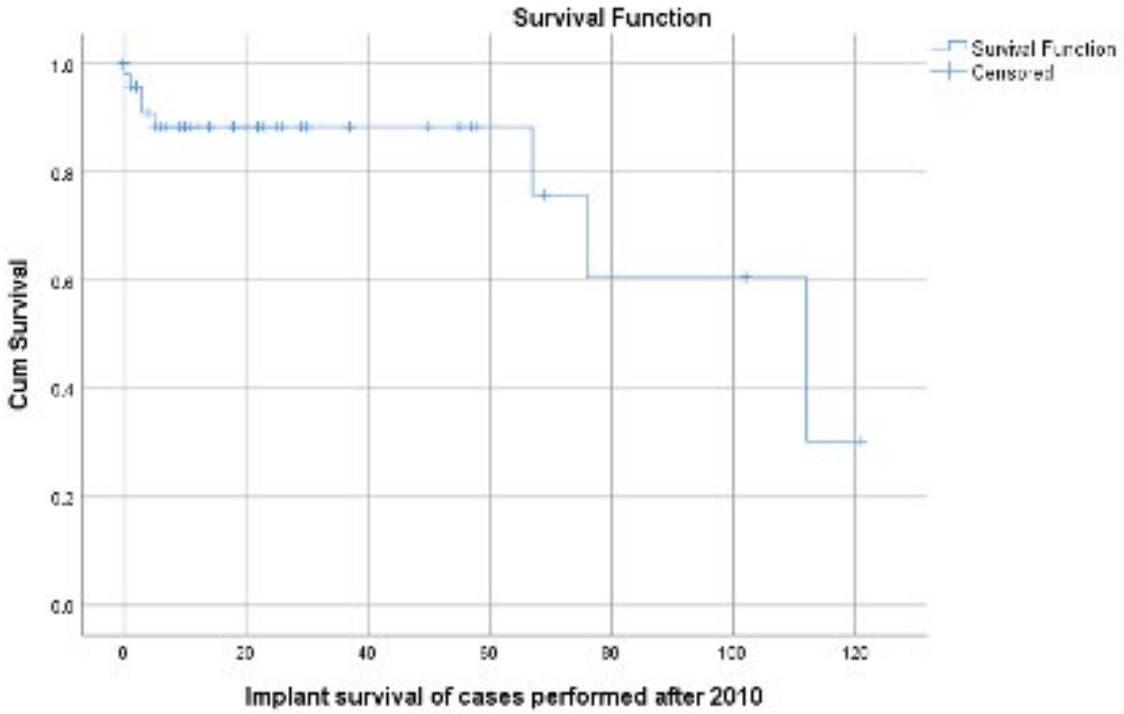


Figure 2. Cumulative implant survival after 2010: Kaplan and Meier device-related survival estimates for all cases performed after 2010, as measured from time of modular endoprosthesis placement to an end point of revision, amputation, or last documented time alive in medical record with no complication including revision having occurred.



Poster #164 3463926

LURBINECTEDIN IN COMBINATION WITH IRINOTECAN IN PATIENTS (PTS) WITH SOFT TISSUE SARCOMAS (STS)

Gregory M. Cote[2], *Santiago Ponce*[3], *Alejandro F. Falcon*[4], *Inmaculada Sánchez Simón*[3], *Elisabeth Jimenez*[3], *Rafael Nunez*[1], *Javier Gómez*[1], *Jesús R Fernández*[1], *Martin Cullell-Young*[1], *Carmen Kahatt*[1], *Ali Zeaiter*[1], *Luis Paz-Ares*[3]
[1]*PharmaMar, Madrid, Colmenar Viejo, SPAIN;* [2]*Massachussets General Hospital, Boston, Massachusetts, UNITED STATES;* [3]*Hospital Universitario 12 de Octubre, Madrid, SPAIN;* [4]*Hospital Universitario Virgen del Rocio, Sevilla, SPAIN*

Objective: Lurbinectedin is a new agent that exerts antitumor activity through inhibition of trans-activated transcription and modulation of the tumor microenvironment. Preclinical synergism/additivity in combination with irinotecan has been reported, thus prompting the initiation of this phase I/II trial.

Methods: This ongoing trial is evaluating lurbinectedin in combination with irinotecan in pts with advanced solid tumors. The trial is divided in two stages. In a phase I stage, pts are being enrolled following a standard 3+3 dose escalation design in 2 cohorts: Cohort A (Lurbinectedin escalation group: lurbinectedin at escalating doses on Day [D] 1 plus a fixed dose of irinotecan 75 mg/m2 on D1 and D8 every 3 weeks [q3w]), and Cohort B (Irinotecan escalation group: irinotecan at escalating doses on D1 and D8 plus a fixed dose of lurbinectedin 3 mg/m2 on D1 q3w). Dose escalation in Cohort A has been finished (the recommended dose [RD] has been achieved). At the present, patient accrual is ongoing at expansion of Cohort A and at dose escalation of Cohort B. A phase II expansion stage will evaluate the recommended dose (RD) in those indications with early evidence of antitumor activity during the phase I stage. Results in the subgroup of pts with STS are presented here.

Results: 21 pts with advanced STS were treated at 6 dose levels (DL): 17 pts in Cohort A (11 at the RD of irinotecan 75 mg/m2 + lurbinectedin 2 mg/m2 + G-CSF; and 6 at DLs other than the RD) and 4 pts at all DLs in Cohort B. Among pts with STS, 67% were males; 33% had ECOG PS of 1; the median age was 55 years (range, 19-75 years); and the median number of prior chemotherapy lines for advanced disease was 2 (range, 0–4) per pt. Histological subtypes were synovial sarcoma (n=6 pts), leiomyosarcoma (n=5), liposarcoma (n=3), Ewing sarcoma (n=2), chordoma (n=2), extraskeletal myxoid chondrosarcoma, carcinosarcoma and myoepithelial carcinoma (n=1 each).
Four protocol-defined dose-limiting toxicities (DLTs) were reported in STS pts during dose escalation in Cohort A: one episode of febrile neutropenia and 3 omissions of irinotecan D8 infusion due to grade (G) 3 neutropenia (n=2) or G4 neutropenia (n=1). No DLTs occurred in the 4 pts treated in Cohort B.
At the RD of Cohort A (n=11 pts), common G1/2 toxicities were nausea, vomiting, fatigue, diarrhea, anorexia and rash; G3/4 toxicities were neutropenia in 9 pts (G3 in 5 pts, G4 in 4 pts); anemia in 2 pts; and thrombocytopenia and diarrhea in 1 pt each. No episodes of febrile neutropenia occurred at the RD.
No objective responses per RECIST were documented. Prolonged stable disease (SD >4 months) was observed in 9 of 20 evaluable pts (clinical benefit rate: 45%). Six of these 9 pts showed a decrease in their tumor size (target lesions). Overall, 7 of 20 pts (35%) were progression-free at 6 months. The disease control rate was 70%.
In synovial sarcoma pts, prolonged SD was observed in 3 of 6 pts. At the present, 2 pts are still on treatment, with clinical benefit after 12 and 16 months, respectively, and with progression.

Conclusion: Myelosuppression was a DLT, but was predictable and manageable. Early evidence of antitumor activity was observed, especially in pts with synovial sarcoma. The RD defined for Cohort A (irinotecan 75 mg/m2 + lurbinectedin 2 mg/m2 + G-CSF) is being evaluated in a sarcoma cohort during the phase II expansion stage.

Poster #165 3463955

SPATIAL DETECTION OF CELLULAR CROSS-PRESENTATION AS A PROGNOSTIC TOOL IN SOFT TISSUE SARCOMA

Monika Ehnman[1], *Panagiotis Tsagkozis*[2], *Yanhong Su*[1], *Nicholas P. Tobin*[1], *Okan Gultekin*[3], *Anna Malmerfelt*[1], *Katrine Ingelshed*[3], *Johanna Lundquist*[1], *Wiem Chaabane*[1], *Maya H. Nisancioglu*[1], *Lina W. Leiss*[1], *Arne Östman*[1,4], *Jonas Bergh*[1,5], *Kaisa Lehti*[3,6], *Saikiran Sedimbi*[3], *Felix Haglund*[1]

[1]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, SWEDEN; [2]Department of Molecular Medicine and Surgery, Karolinska Institutet and Muskuloskeletal Tumor Service, Karolinska University Hospital, Stockholm, SWEDEN; [3]Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, SWEDEN; [4]Centre for Cancer Biomarkers CCBIO, University of Bergen, Bergen, NORWAY; [5]Department of Oncology-Pathology, Karolinska Institutet, Radiumhemmet, Karolinska University Hospital, Stockholm, SWEDEN; [6]Department of Biomedical Laboratory Science, Norwegian University of Science and Technology, Trondheim, NORWAY

Objective: Immune cells can be powerful regulators of tumor growth and disease progression. Yet, the potential role of professional antigen presenting cells (APCs) in soft tissue sarcoma (STS) is poorly explored. It is also becoming increasingly clear that scoring systems for molecular biomarkers that are useful on an individual case basis are largely lacking.

In this study, we aimed to:
1. Demonstrate that spatial detection of cell-cell interactions between CD11c+ conventional dendritic cells (cDCs) and CD8+ T cells is prognostic
2. Explore whether the prognostic signal is maintained across subtypes
3. Characterize the prognostic signal in different tumor microenvironments (TMEs)

Methods: Formalin-fixed, paraffin-embedded tissue (FFPE) from two independent soft-tissue sarcoma cohorts (N=78, Karolinska University Hospital) was stained by multiplex immunohistochemistry (IHC) and scored for direct cell-cell interactions between CD11c+ cDCs and CD8+ T cells. Spatial distribution of Foxp3+ cells was explored together with tertiary lymphoid structure (TLS) abundance. Relative levels of PD1 expression in CD8+ T cells was determined by Opal multiplexing (immunofluorescence) followed by digital image analysis. The Pan-Can/sarcoma cohort (N=259) was used for exploring the ITGAX (CD11c)/CD8A (CD8) 2-gene signature by contrast group analysis considering different molecular TME settings.

Results: Spatial detection of direct cell-cell interactions between CD11c+ cDCs and CD8+ T cells was prognostic for improved metastasis-free survival (P=0.019, log-rank test) as well as overall survival (P=0.049, log-rank test) (STS cohort 1, 30 patients, Karolinska University Hospital). Neither of the two markers was prognostic alone. In a validation cohort of dedifferentiated/well-differentiated liposarcoma (cohort 2, 48 patients, Karolinska University Hospital), the overall survival benefit of intratumoral cell-cell interactions was confirmed (P=0.040, log-rank test). In contrast, peritumoral interactions, in the absence of intratumoral interactions, were strongly associated with worse prognosis (P=0.0001, log-rank test).

Supportive evidence from a contrast group analysis of gene expression data (cohort 3, 259 patients, Pan-Can/sarcoma) revealed that high expression levels of ITGAX (CD11c) together with CD8A (CD8) were prognostic for improved overall survival (P=0.0052, log-rank test). This prognostic signal was maintained in a Foxp3^{high} TME. Moreover, tissue analysis of CD8+ T cells in the Karolinska cohorts demonstrated that PD1 protein expression varied extensively between cells, indicating the existence of a subpopulation with a non-exhausted phenotype. Importantly, TLSs were predominantly found in smaller tumors (P=0.032, Mann-Whitney U test), and were always positive for CD11c-CD8 interactions. However, they displayed different patterns of Foxp3 cell infiltration.

Conclusion: Altogether, the study has identified clinically relevant alterations in the immune TME linked to patient survival. Direct cell-cell interactions between marker-defined cDCs and T cells emerge as an attractive prognostic tool, and should be further explored as a potential biomarker. Notably, direct cell-cell interactions can easily be visualized by multiplex IHC and scored with low inter- and intraobserver variability. We are currently exploring other bonafide DC and CD8 T cell markers to further confirm and characterize the presence of these cells in the TME of additional patient cohorts.

Poster #166 3464017

DEMOGRAPHICS AND OUTCOME OF PATIENTS WITH ADULT HEAD AND NECK SARCOMA: THE OTTAWA EXPERIENCE

*Taylor Barrett[1], **Samy El-Sayed**[2], Prudence Buchanan[1], Ionut Busca[1]*
[1]The Ottawa Hospital Research Assistant, Ottawa, Ontario, CANADA; [2]University of Ottawa, Ottawa, Ontario, CANADA

Objective: Malignant head and neck soft tissue sarcomas are rare. It accounts for only 1% of all head and neck malignancies. Literature are scarce and reported experiences are limited. Here we report a teaching centre experience in Ontario.

Methods: This study is part of the retrospective sarcoma database project. Ethics approval was obtained. All patients with malignant soft tissue sarcomas of the head and neck region seen in Ottawa during the period from 2005 to 2014 were captured. All patient's information electronic or otherwise were reviewed. Data collected included patient's demographics, diagnostics and staging information, adverse events and survival by treatment. Data were entered into the REDCAP program. Kaplan-Meier analysis for survival and outcome were obtained.

Results: During that period 36 patients with head and neck soft tissue sarcoma were seen. Median age was 75 years. Male to female ratio was 2:1. All head and neck sites were affected but the majority were in the ear, face and scalp. 70% of tumours measured less than 5 cm. 40% were low grade tumours. All histological subtypes existed but the visible minority was fibrosarcomas and malignant fibrous histiocytomas. With a median follow up of 3.6 years, all events occurred in the first 5 years with median recurrence free survival of 5 years and 5-year overall survival of 56%.

Conclusion: Head and neck soft tissue sarcomas are rare accounting for only 5-10% of all soft tissue sarcomas which account for 0.7% of all malignancies. Published literature are limited and span over a long period of time where much have changed in diagnosis, staging and treatment. Our study has the advantage of looking at a well-defined recent period of time but again highlights the fact that we are dealing with multiple histology, biology and sites in that rare condition.

Poster #167 3464033

RIPRETINIB DEMONSTRATED ACTIVITY ACROSS ALL KIT/PDGFRA MUTATIONS IN PATIENTS WITH FOURTH-LINE ADVANCED GASTROINTESTINAL STROMAL TUMOR: ANALYSIS FROM THE PHASE 3 INVICTUS STUDY

Patrick Schöffski[1], *Sebastian Bauer*[2], *Michael Heinrich*[3], *Suzanne George*[4], *John Zalcberg*[5], *Hans Gelderblom*[6], *César Serrano*[7], *Robin L. Jones*[8], *Steven Attia*[9], *Gina D'amato*[10], *Ping Chi*[11], *Peter Reichardt*[12], *Julie Meade*[13], *Kelvin Shi*[13], *Ying Su*[13], *Rodrigo Ruiz-Soto*[13], *Margaret von Mehren*[14], *Jean-Yves Blay*[15]

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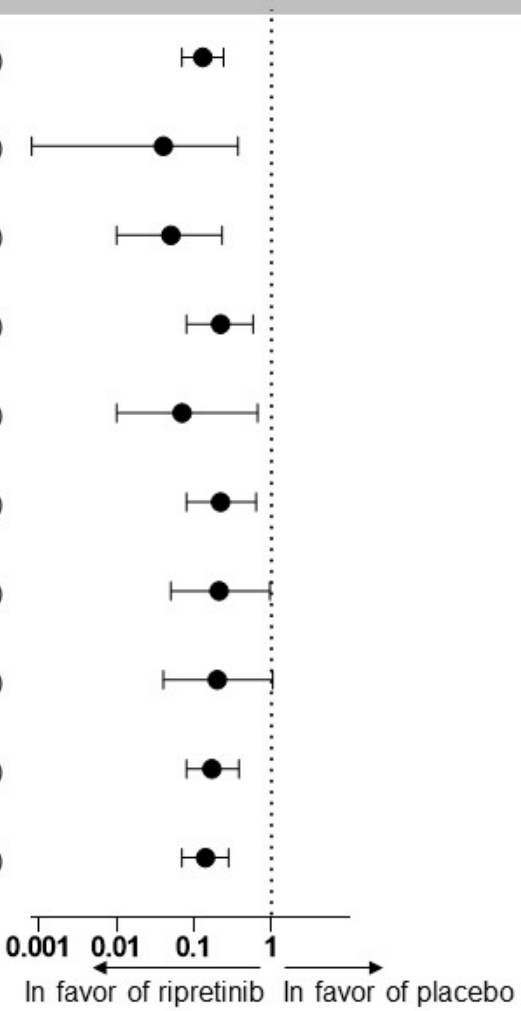
Objective: Ripretinib is a switch-control tyrosine kinase inhibitor designed to broadly inhibit mutant KIT/PDGFRA kinases which was recently approved by the FDA for patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib. In INVICTUS (NCT03353753), a phase 3, randomized, double-blind, placebo-controlled trial, patients with advanced GIST who were previously treated with at least imatinib, sunitinib, and regorafenib were randomized (2:1) to ripretinib 150 mg once daily (QD) or placebo. Ripretinib significantly improved progression-free survival (PFS) compared with placebo (6.3 vs 1.0 months, hazard ratio [HR] 0.15, P <0.0001) reducing the risk of disease progression or death by 85% and showed a clinically meaningful improvement in overall survival (15.1 vs 6.6 months, HR 0.36). Ripretinib is associated with a well-tolerated safety profile. Here, we report the results of an exploratory analysis from INVICTUS assessing the efficacy of ripretinib across KIT/PDGFRA mutation subgroups.

Methods: Tumor biopsies were collected after patients received their last anticancer therapy prior to study entry and were sequenced using a next-generation sequencing (NGS) panel (324 genes). Liquid biopsies (plasma circulating tumor DNA [ctDNA]) were collected pre-dose on Cycle 1 Day 1 and profiled using an NGS liquid biopsy assay (73 genes). Both assays have full coverage of KIT and PDGFRA genes. Mutation subgroups were determined by KIT/PDGFRA mutations obtained by combining results from tumor and liquid biopsies (ctDNA). In this exploratory analysis, correlations between KIT/PDGFRA mutational status and clinical outcomes were assessed. The data cutoff for this analysis was May 31, 2019. Updated analyses will be presented at the meeting.

Results: Overall, 129 patients enrolled in the study (ripretinib 150 mg QD, n = 85; placebo, n = 44). KIT/PDGFRA mutation status was identified in a total of 124 patients (96.1%) using tumor and ctDNA, of whom 115 had KIT/PDGFRA mutations (KIT mutant, n = 112; PDGFRA mutant, n = 3) and 9 had no mutation in KIT/PDGFRA genes. Ripretinib demonstrated clinical benefit in PFS for patients with any KIT exon 9/11/13/17 mutations when compared to placebo (**Figure**). Due to low numbers, patients with any KIT exon 14 (n = 6) or any KIT exon 18 (n = 6) mutations were excluded from this analysis. The 3 patients with PDGFRA mutations (all non-D842V exon 18 mutations) that received ripretinib showed a PFS of 0.9, 1.7, and 6.5 months. Among 10 patients who were KIT/PDGFRA wild type by tumor tissue, 7 received ripretinib and had a median PFS of 6.0 months vs a median of 2.1 months in 3 patients receiving placebo.

Conclusion: In this exploratory analysis, ripretinib demonstrated clinically meaningful activity in patients with fourth-line advanced GIST with multiple, heterogeneous genetic subsets of KIT mutations. Overall, these results provide evidence that ripretinib can inhibit a broad spectrum of KIT/PDGFRA mutations in patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

Mutation subgroup	Ripretinib 150 mg QD (N)	Placebo (N)	Hazard ratio (95% CI)
Any KIT Exon 11[a]	52	34	0.13 (0.07, 0.24)
Exon 11 + 13	8	5	0.04 (0.00, 0.37)
Exon 11 + 17	20	14	0.05 (0.01, 0.23)
Exon 11 + 13 + 17	16	9	0.22 (0.08, 0.58)
Others[b]	8	6	0.07 (0.01, 0.66)
Any KIT Exon 9[a]	16	7	0.22 (0.08, 0.63)
Exon 9 + 17	7	4	0.21 (0.05, 0.95)
Others[c]	9	3	0.20 (0.04, 1.03)
Any KIT Exon 13	27	16	0.17 (0.08, 0.38)
Any KIT Exon 17	44	27	0.14 (0.07, 0.28)



[a]One patient had both KIT exon 11 and KIT exon 9 mutations detected in liquid biopsy.
[b]Positive for KIT exon 11 mutation and negative for KIT exon 13 and exon 17 mutation
[c]Positive for KIT exon 9 mutation and negative for KIT exon 17 mutation

Poster #168 3464034

REFINING THE APPROACH TO PATIENTS WITH PRIMARY SOFT TISSUE SARCOMA OF THE EXTREMITIES AND TRUNK WALL (ESTSTS): OUTCOME IMPROVEMENT OVER 30 YEARS AT A SINGLE INSTITUTION

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Objective: In 2011 we reported an improvement of outcome over time in patients with extremity soft tissue sarcoma treated at our center between 1987 and 2007. We have now updated the analysis at a later FU to assess possible further changes in survival of extremity and superficial trunk soft tissue sarcoma (ESTSTS) patients in the recent years.

Methods: Patients with primary localized adult-type ESTSTS surgically treated at our institution between 1987 and 2017 were retrospectively reviewed and categorized into six 5-year groups according to the date of primary surgery, from 1987-1992 (group 1) to 2013-2017 (group 6). Crude cumulative incidence (CCI) of sarcoma-specific mortality (SSM), local recurrence (LR), and distant metastases (DMs) were calculated for each time period in a competing risks framework. Metastasis-free survival (MFS) was calculated for each group taking into account all DMs (either occurred as first or later).

Results: A total of 2384 adult ESTSTS patients were identified. Median overall follow-up was 104 months (mo), median overall post-metastasis follow-up was 76mo. Clinicopathologic characteristics by group are summarized in Table 1. Five-year CCI-SSM decreased from 26% in group 1 to 12% in group 6 ($p < 0.001$). Five-years CCI-LR also decreased from 14% in group 1 to 7% in group 3 and then plateaued until group 6. CCI-DM did not change over time. However, 5-yrs MFS raised significantly over time from 60% in group 1 to 72% in group 4 and levelled up in groups 5 and 6 ($p = 0.040$). Similarly, although not in a significant manner, post DM median survival in groups 4 to 6 was always higher than in groups 1 to 3, ranging from 15% in group 1 to 28.9% in group 4. Of note, the use of preoperative chemotherapy increased from 18% in group 1 to 29% in group 6. Similarly, preoperative radiotherapy use increased from 1.6% in group 1 to 26% in group 6.

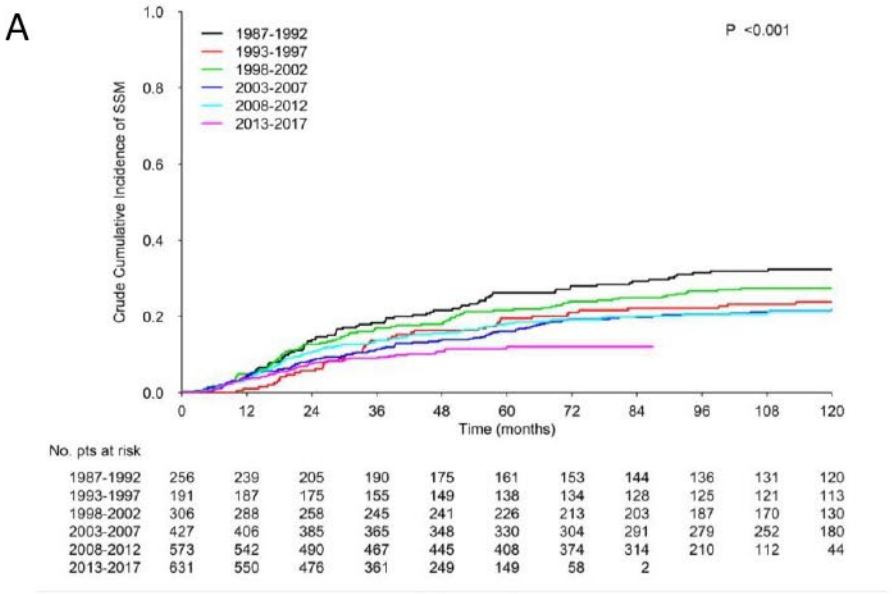
Conclusion: An improvement in CCI of LR and SSM was observed over time, with the best outcomes observed in the last 15 years (group 4-6). This was paralleled by an increased use of preoperative radiotherapy and chemotherapy. An integrated approach may have contributed to the improvement in local and distant control, and hence SSM. Post-DM outcome has also improved in the recent 15 years, possibly thanks to the availability of different new systemic agents and techniques for local therapies.

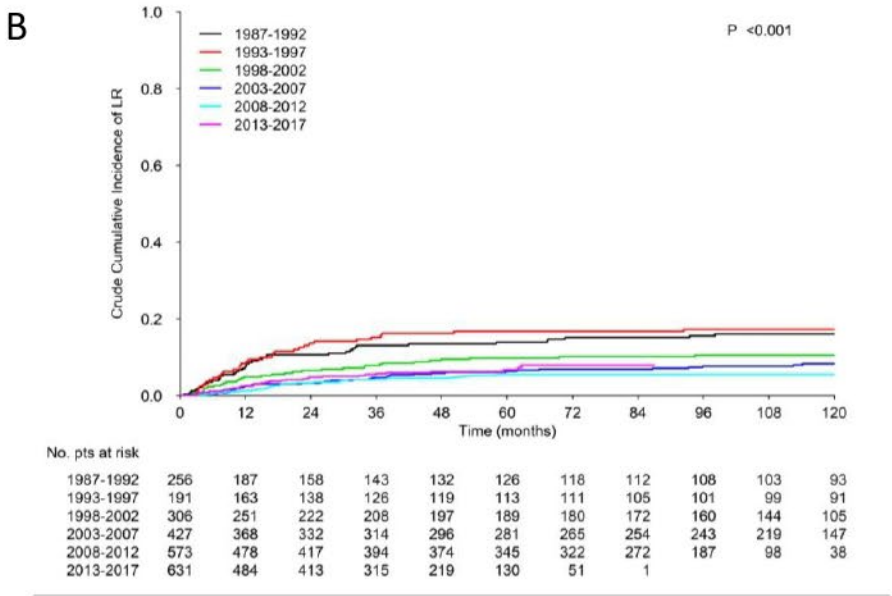
Main patients and tumors characteristics according to study groups.

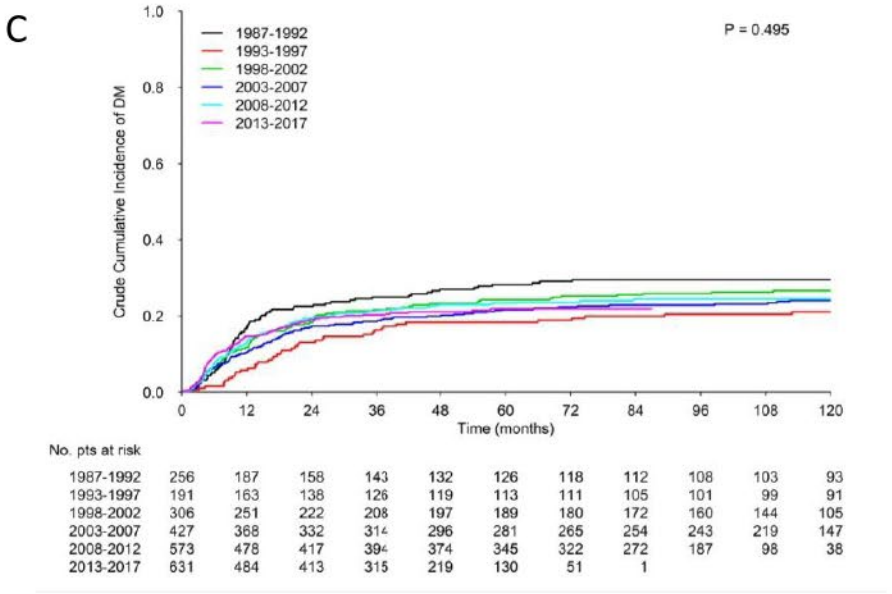
Group	Overall	1987-1992	1993-1997	1998-2002	2003-2007	2008-2012	2013-2017	SMD
N	N = 2384	N = 256	N = 191	N = 306	N = 427	N = 573	N = 631	
Male Female	1310 (54.9%) 1074 (45.1%)	139 (54.3%) 117 (45.7%)	94 (49.2%) 97 (50.8%)	177 (57.8%) 129 (42.2%)	226 (52.9%) 201 (47.1%)	310 (54.1%) 263 (45.9%)	364 (57.7%) 267 (42.3%)	0,077
Age [years], Median (inter-quartile range)	54.00 (40.00; 66.00)	47.00 (34.00; 59.25)	50.00 (36.50; 61.00)	54.00 (36.00; 66.00)	53.00 (38.00; 65.00)	57.00 (44.00; 69.00)	57.00 (44.00; 68.00)	0,251
Tumor size [cm], Median (inter-quartile range)	7.00 (4.00; 10.00)	8.00 (4.00; 12.00)	6.00 (4.00; 10.00)	6.00 (4.00; 10.00)	6.00 (4.00; 11.00)	6.00 (4.00; 11.00)	7.00 (5.00; 11.00)	
Tumor site								0,262
Upper limb	329 (13.8%)	37 (14.5%)	24 (12.6%)	53 (17.3%)	65 (15.2%)	73 (12.7%)	77 (12.2%)	
Superficial trunk	214 (9.0%)	3 (1.2%)	8 (4.2%)	29 (9.5%)	52 (12.2%)	52 (9.1%)	70 (11.1%)	
Girdle	561 (23.5%)	59 (23.0%)	52 (27.2%)	53 (17.3%)	94 (22.0%)	143 (25.0%)	160 (25.4%)	
Lower limb	1280 (53.7%)	157 (61.3%)	107 (56.0%)	171 (55.9%)	216 (50.6%)	305 (53.2%)	324 (51.3%)	
Depth								0,378
Superficial	652 (27.3%)	20 (7.8%)	18 (9.4%)	100 (32.7%)	160 (37.5%)	185 (32.3%)	169 (26.8%)	
Deep	1732 (72.7%)	236 (92.2%)	173 (90.6%)	206 (67.3%)	267 (62.5%)	388 (67.7%)	462 (73.2%)	
Grade								0,242
I	504 (21.1%)	36 (14.1%)	47 (24.6%)	82 (26.8%)	90 (21.1%)	128 (22.3%)	121 (19.2%)	
II	629 (26.4%)	44 (17.2%)	57 (29.8%)	102 (33.3%)	116 (27.2%)	146 (25.5%)	164 (26.0%)	
III	1251 (52.5%)	176 (68.8%)	87 (45.5%)	122 (39.9%)	221 (51.8%)	299 (52.2%)	346 (54.8%)	
Surgical margins								89 (14.1%)
R0	2082 (87.3%)	221 (86.3%)	164 (85.9%)	279 (91.2%)	377 (88.3%)	499 (87.1%)	542 (85.9%)	
R1	302 (12.7%)	35 (13.7%)	27 (14.1%)	27 (8.8%)	50 (11.7%)	74 (12.9%)	89 (14.1%)	
Chemotherapy								0,389
None	1776 (74.5%)	207 (80.9%)	170 (89.0%)	250 (81.7%)	298 (69.8%)	423 (73.8%)	428 (67.8%)	
Pre w/o Post	466 (19.5%)	46 (18.0%)	11 (5.8%)	22 (7.2%)	95 (22.2%)	109 (19.0%)	183 (29.0%)	
Post only	142 (6.0%)	3 (1.2%)	10 (5.2%)	34 (11.1%)	34 (8.0%)	41 (7.2%)	20 (3.2%)	
Radiotherapy								0,585
None	1336 (56.0%)	168 (65.6%)	121 (63.4%)	150 (49.0%)	172 (40.3%)	325 (56.7%)	400 (63.4%)	
Pre w/o Post	303 (12.7%)	4 (1.6%)	0 (0.0%)	9 (2.9%)	51 (11.9%)	75 (13.1%)	164 (26.0%)	
Post only	745 (31.2%)	84 (32.8%)	70 (36.6%)	147 (48.0%)	204 (47.8%)	173 (30.2%)	67 (10.6%)	
Amputation	61 (2.6%)	26 (10.2%)	4 (2.1%)	8 (2.6%)	5 (1.2%)	5 (0.9%)	13 (2.1%)	0,166
Reconstructive procedures	562 (23.6%)	27 (10.5%)	11 (5.8%)	51 (16.7%)	101 (23.7%)	164 (28.6%)	208 (33.0%)	0,350

Abbreviations: w/o, with or without.

IMAGE CAPTION:
Figure 1. CCI-SSM (panel A), CCI-LR (panel B) and CCI-DM (panel C) according to study groups.







Poster #169 3464091

CARDIOTOXICITY AMONG PATIENTS WITH SARCOMA TREATED WITH DOXORUBICN: A REAL-WORLD DATABASE STUDY

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Objective: Doxorubicin (DOX) continues to play a role in management of patients with sarcoma, particularly those with advanced disease. Dose-dependent cardiomyopathy is a challenge in its use. Strategies have been proposed to mitigate this risk, including administration by continuous intravenous (CIV) infusion as an alternative to bolus (BOL) administration. This study used real world data to explore the impact of DOX mode of administration on cardiotoxicity outcomes, duration of DOX administration, and time to treatment failure (TTF).

Methods: This study used IBM MarketScan claims to identify patients age ≥ 18 who received at least 2 DOX administrations (excluding liposomal DOX) after sarcoma diagnosis. Patients with history of cardiac events as evidenced by International Classification of Disease (ICD) codes in the database prior to DOX use were excluded. Cardiac events after initiation of DOX were compared for BOL versus CIV overall, by tumor site and by regimen during three follow-up periods, early (within 1 year), middle (>1 to 5 years) and late (>5 years), from DOX initiation using Fisher's exact test. Duration of DOX, measured from the first to last infusion, and TTF, defined as time from initiation of DOX to subsequent systemic therapy, hospice or death, were evaluated using Kaplan-Meier method and unadjusted Cox proportional hazards models.

Results: A total of 1,734 patients with sarcoma met eligibility criteria (890 with metastatic codes). The most common regimen used was DOX plus ifosfamide (n=481, 27.7%), followed by DOX monotherapy (n=461, 26.6%). Most patients had codes for both modes of infusion on the same claim date and could not be definitely assigned to BOL or CIV infusion groups using billing codes; however, 196 and 399 patients had exclusive BOL and CIV codes, respectively. Among patients receiving DOX monotherapy with exclusive codes, 170 and 82 had exclusive BOL and CIV codes, respectively. For patients with exclusive infusion type codes, the mean duration (±standard deviation) of DOX treatment was significantly different for BOL vs CIV overall (72.7 ±97.1 vs 98.3 ±201.2 days, p=0.04). Duration of DOX monotherapy was 68.3 ±92.4 days for BOL vs 68.8 ±62.3 days for CIV, p=0.96. Overall, cardiac events for BOL vs CIV were 11.2% vs 7.5% (p=0.13) during the early period, 7.7% vs 4.0%, (p=0.06) during the middle period, and 1.0% vs 0.5% (p=0.60) in the late period. There were no differences in cardiac events for BOL vs CIV among those treated with DOX monotherapy (p=0.16, 0.93 and 1.0 for the early, middle, and late period, respectively). TTF was significantly different by mode of administration (BOL vs CIV hazard ratio [HR]=0.76, 95% confidence interval [CI]: 0.63-0.90, p=0.002), with median TTF of 226 days (95% CI: 192-320) for BOL vs 171 days (95% CI: 142-192 days) for CIV. For DOX monotherapy, TTF was also significantly different for BOL (median 266 days, 95% CI: 192-320) vs CIV (median 227 days, 95% CI: 177-335); HR=0.72 95% CI: 0.54-0.95 p=0.02.

Conclusion: These data do not show evidence of differences in cardiotoxicity by mode of infusion. However, TTF was significantly different by mode of administration, with BOL having longer TTF. Duration of DOX treatment was shorter for BOL vs CIV overall, but there were no differences for duration of DOX monotherapy by mode of administration. However, the role of combination vs monotherapy is not fully evaluated and may play a role in these findings. The retrospective nature of this study limits the determination of a causal relationship between these factors. Despite this limitation, these data do not suggest differential cardiac toxicity outcomes by mode of DOX infusion, but rather that cardiac toxicity is associated with the duration of exposure. This may reflect cumulative DOX exposure, a known correlate of cardiac toxicity, but this is not verified. Additional adjusted analyses are needed to verify that CIV DOX administration may not translate into decreased cardiotoxicity in the real-world setting.

Poster #170 3464158

NOVEL GENE FUSIONS IN PEDIATRIC RHABDOMYOSARCOMAS

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Objective: Rhabdomyosarcoma is a malignant mesenchymal neoplasm with skeletal muscle differentiation as defined by histologic and/or immunohistochemical features. Rhabdomyosarcomas are subclassified as embryonal, spindle cell/sclerosing, alveolar, and pleomorphic. These rhabdomyosarcoma subtypes can be further characterized by genetic features. Thus, alveolar rhabdomyosarcomas may show PAX3-FOXO1 or PAX7-FOXO1 gene fusions or may be fusion negative. Similarly, spindle cell/sclerosing rhabdomyosarcomas may show MYOD1 mutations or fusions involving VGLL1 and NCOA2 genes. Here, we describe 2 gene fusions that have not previously been reported in rhabdomyosarcomas.

Methods: Case 1. A 1-year-old boy presented with a left leg swelling. MRI showed a mass in the left proximal thigh centered within the vastus lateralis muscle and another mass in the left retroperitoneum. Fine needle aspiration and core needle biopsies of the left thigh mass showed an epithelioid neoplasm with diffuse cytoplasmic staining for desmin and focal nuclear staining for myogenin and myoD1, morphologically consistent with epithelioid rhabdomyosarcoma.

Case 2. A 4-year-old boy presented with left orbital swelling that was biopsied at an outside institution. Histopathologic review showed an infiltrative cellular neoplasm with round to spindle cells in a collagenous stroma with diffuse cytoplasmic staining for desmin and diffuse nuclear staining for myogenin (strong) and myoD1 (weak to moderate intensity), consistent with rhabdomyosarcoma that did not clearly fit with any of the known histologic subtypes.

Next generation sequencing. For both cases, total RNA was isolated from a representative FFPE block and library preparation was performed using Archer RNA Fusion v1 Custom FusionPlex® Kit (ArcherDx). The assay targets regions of 93 genes known to be associated with fusions in pediatric neoplasms. Massively parallel sequencing was performed on the Illumina MiSeq instrument. The analysis and fusion/variant detection was performed using the Archer Unlimited software (ArcherDx). RNA sequences used as references (hg19 (GRCh37)) are available on the NCBI website (http://www.ncbi.nlm.nih.gov/).

Results: Next generation sequencing identified a NSD3 (exon 8) – FOXO1 (exon 2) fusion in case 1 and a PAX8 (exon 8) – PPARG (exon 2) fusion in case 2. While PAX8-PPARG fusion is well-described in thyroid carcinoma, it has not previously been reported in rhabdomyosarcoma. NSD3-FOXO1 fusion is a novel, previously unreported fusion. We are currently creating recombinant skeletal muscle and mesenchymal stem cell lines that stably express these fusion genes to study their transformation potential.

Conclusion: NSD3-FOXO1 and PAX8-PPARG are novel fusions in pediatric rhabdomyosarcomas.

Poster #171 3464160

A NOVEL PATIENT-DERIVED, AGGRESSIVE, EXTRAOSSEOUS EWING SARCOMA CELL LINE

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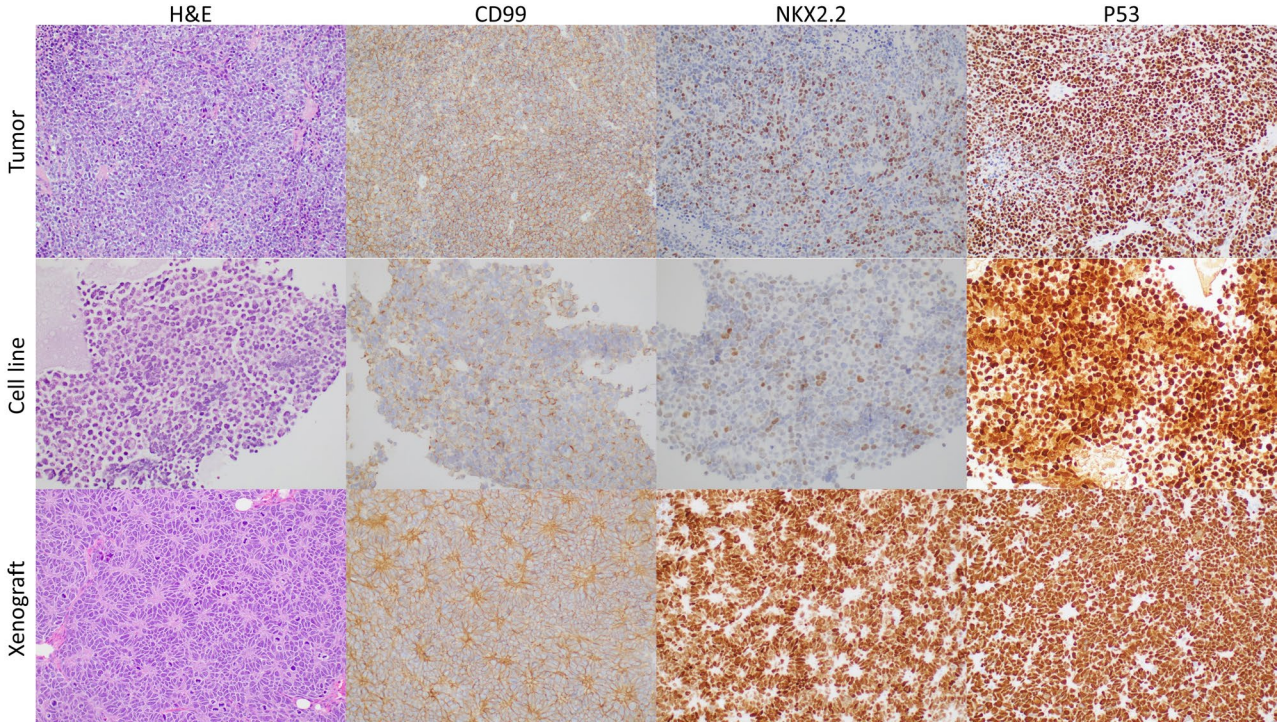
Objective: Ewing sarcoma is the 2nd most common malignant bone tumor in children and adolescents. It is characterized by fusions involving members of the FET and ETS gene families, with EWSR1-FLI1 fusion [t(11;22)] being the most common (85% of cases). TP53 mutations occur in ~7% of Ewing sarcomas and correlate with worse outcomes. Models for TP53 mutated, EWSR1-FLI1 positive Ewing sarcoma may be critical to illuminate the role of TP53 in disease progression.

Methods: The cell line, designated CMC-931, was derived from a recurrent (post-chemoradiotherapy), aggressive Ewing sarcoma with t(11;22) that first arose in the soft tissues of the buttock in a pediatric patient. The cells were plated in 2D monolayer culture (Minimum Essential Medium, 3% FBS, 1% Insulin-Transferrin-Selenium) and did not senesce after more than 80 passages (doubling time ~21 hours). The cells were interrogated for translocations by next generation RNA sequencing and for TP53 mutations by Sanger sequencing. Five million cells were injected subcutaneously into the flanks of NOD/SCID/gamma mice. The original tumor, cell line, and mouse xenograft were studied by histology and immunohistochemistry.

Results: Next generation RNA sequencing showed the cells to harbor EWSR1-FLI1 fusion, and Sanger sequencing showed TP53 mutation (p.R280K) with loss of heterozygosity. Tumors were palpable in mice within 4 weeks and grew to >1.5 cm^3 by 8 weeks. The xenograft histology showed malignant small round cell neoplasm with rosettes. Immunostains showed characteristic membranous CD99 and nuclear NKX2.2 in formalin-fixed/paraffin-embedded sections of the original tumor, cell line, and xenograft, all of which also showed nuclear P53 immunopositivity consistent with loss of function TP53 mutation (Figure 1).

Conclusion: We have established CMC-931, a novel patient-derived, EWSR1-FLI1 positive, TP53 mutant, aggressive, extraosseous Ewing sarcoma cell line, which readily forms tumors in mice.

Figure 1



Poster #172 3464216

SOFT-TISSUE SARCOMA IN ELDERLY PATIENTS: PATTERNS OF CARE AND SURVIVAL

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Objective: The aim of this study was to evaluate patterns of care and survival in elderly soft tissue sarcoma patients over 80-year-old and their impact on the outcome.

Methods: We retrospectively reviewed the data of 69 patients diagnosed with soft tissue sarcoma between 2011 and 2019. Patients were divided into two groups: patients <80 years old (n=55) and patients ≥80 years old (n=14). Treatment plan, margin, local recurrence and overall survival were compared between groups. Kaplan-Meier method (Log-rank test) was performed to investigate the survival rate.

Results: Radical surgery was performed a little bit more in the patients of ≥80, (86%) than the patients<80 (77%). Radiotherapy was performed in 31% of elderly patient and 25% of other patients. Chemotherapy were performed only one patient (6%, Eribulin) in the group of ≥80, and 40% in the group <80 years old. R1 resection rate was higher in the patient ≥80 (46%) than the patient <80 (17%). Local recurrence rate was higher in the patient ≥80 (14%) than the patient <80 (5%). In the M0 cases, there are no significant difference in overall survival rate between two groups (p=0.3), but relatively poor prognosis in the patient ≥80 (46%) compared with the patient <80 (63%).

Conclusion: It was difficult for elderly patients to receive chemotherapy. Surgical resection was first choice for the treatment of soft tissue sarcoma of elderly patients, but surgical margin was not enough. Combination with radiotherapy was considered to be important factor to control sarcoma in elderly patient.

Poster #173 3464222

THE FREQUENCY OF TP53 GERMLINE PATHOGENIC VARIANTS IN RHABDOMYOSARCOMA EXHIBITING ANAPLASIA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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Objective: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood. An association between RMS and other early-onset cancers was first described in 1969. This cancer predisposition syndrome became known as Li-Fraumeni Syndrome (LFS) and was subsequently shown to be caused by germline pathogenic variants (PVs) in the TP53 tumor suppressor gene. RMS exhibiting anaplasia was recently reported in a small series to be associated with a high rate of germline TP53 PVs. This study provides an updated estimate of the prevalence of TP53 germline PVs in a large cohort of RMS patients, including those with anaplasia.

Methods: The study population includes patients enrolled on one of five Children's Oncology Group (COG) clinical trials with available central pathology review and TP53 germline data available: D9602 (n=18), D9802 (n=14), D9803 (n=29), ARST0331 (n=61) and ARST0531 (n=117). We assessed the prevalence of TP53 germline PVs in this cohort in association with tumor histology, as well as other associated tumor and patient characteristics.

Results: Among the 239 patients, the median age at diagnosis was 2.8 years (range 0.9 to 3.7 years) and 5.8 years (range 0.2 to 28.3 years) (P=0.0003) for the TP53 PV and the TP53 WT patients, respectively. The overall prevalence of germline TP53 PVs was 3% (n=7). Among 46 patients with RMS with anaplasia, 11% (n=5) carried a germline TP53 PV, compared to 1% (2/193) among patients without anaplasia. The proportion of TP53 PVs in those with diffuse anaplasia and focal anaplasia were 9% (3/34) and 17% (2/12), respectively. Five of seven patients (71%) with TP53 germline PVs in our cohort contained RMS exhibiting anaplasia.

Conclusion: The prevalence of germline TP53 PVs in patients of RMS exhibiting anaplasia is approximately 11%, lower than previously estimated. Most patients with a germline TP53 PV exhibit anaplasia. This prevalence still meets the clinical threshold to consider genetic testing in patients with RMS and anaplasia.

TP53 and Anaplasia

Germline TP53	Anaplasia absent	Anaplasia present	P-value*
Absent	191 (82.0%)	41 (18.0%)	0.0034
Present	2 (29.0%)	5 (71.0%)	

* Fisher Exact test, except for numerical age (2-sample t-test). Unknowns are excluded when present.

Patient Characteristics

Characteristic	Germline TP53 Absent (N=232)	Germline TP53 Present (N=7)	P-value*
Sex			0.44
Male	140 (60.3%)	3 (42.9%)	
Female	92 (39.7%)	4 (57.1%)	
Median age at dx (range)	5.8 (0.2-28.3)	2.8 (0.9-3.7)	0.0003
Age at dx			0.028
<1	14 (6.0%)	2 (28.6%)	
1-9	142 (61.2%)	5 (71.4%)	
10+	76 (32.8%)	0	
Primary tumor site			0.058
Bladder/prostate	27 (11.6%)	1 (14.3%)	
Extremity	21 (9.1%)	4 (57.1%)	
GU, non-bladder/prostate	51 (22.0%)	0	
Head and neck	15 (6.5%)	0	
Intrathoracic	3 (1.3%)	0	
Orbit	17 (7.3%)	0	
Parameningeal	59 (25.4%)	1 (14.3%)	
Retroperineum or Perineum/anus	24 (10.3%)	0	
Trunk	10 (4.3%)	1 (14.3%)	
Other	5 (2.2%)	0	
Tumor size			0.45
≤5 cm	119 (51.3%)	5 (71.4%)	
>5 cm	107 (46.1%)	2 (28.6%)	
Unknown	6 (2.6%)	0	
Histology			0.04
ARMS	73 (31.5%)	0	
ERMS	119 (51.3%)	3 (42.9%)	
BRMS	23 (9.9%)	2 (28.6%)	
Spindle cell	13 (5.6%)	2 (28.6%)	
NOS or Mixed RMS or Unknown	4 (1.7%)	0	

* Fisher Exact test, except for numerical age (2-sample t-test). Unknowns are excluded when present.

Poster #174 3464228

OSTEOSARCOMA HEALTH LITERACY: A QUANTITATIVE ASSESSMENT OF ONLINE PATIENT EDUCATION MATERIAL

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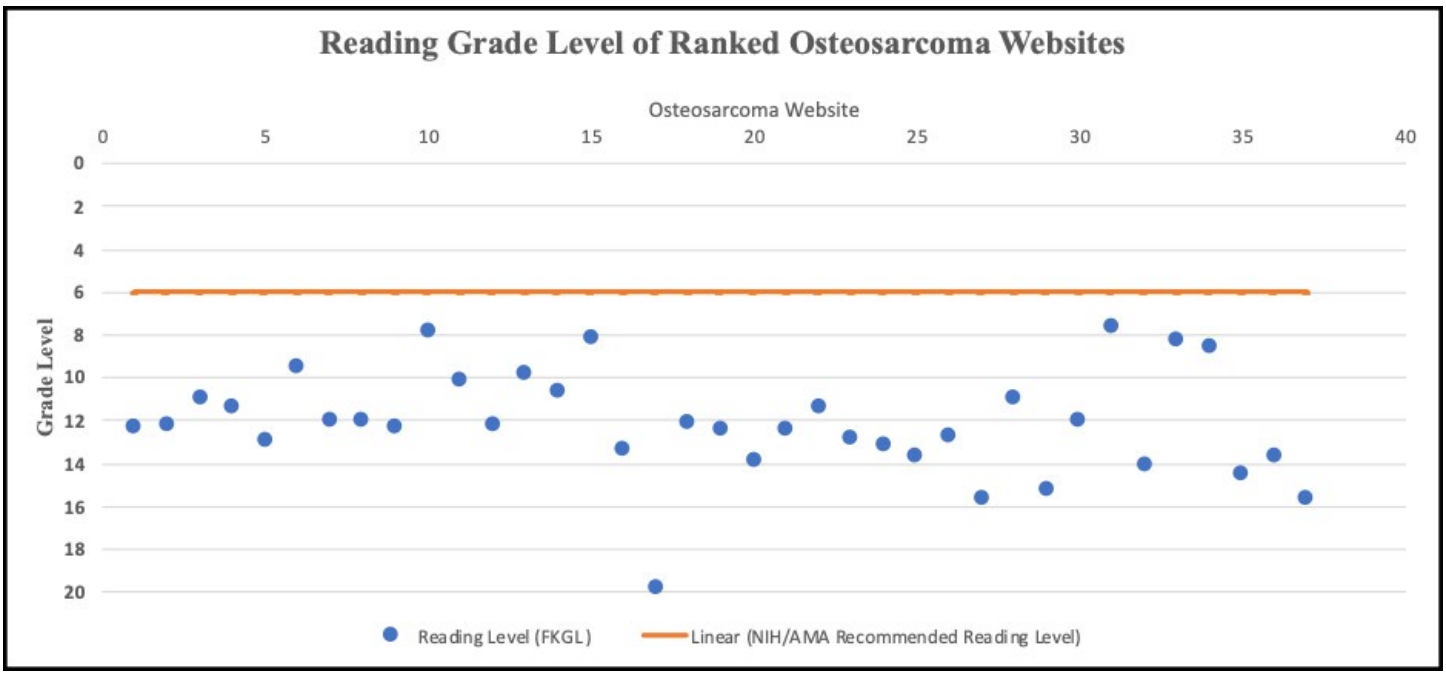
Objective: Patients and their families often turn to online resources following a diagnosis such as osteosarcoma. The American Medical Association (AMA) and National Institutes of Health (NIH) recommend online health information to be written at a 6th grade or lower reading level in order to be fully understood by the average adult in the United States. Prior studies have examined osteosarcoma patient resources to assess syntax reading level, quality of treatment options, and social reach of the materials. However, these analyses have not measured whether the text is written such that readers can process key information (understandability) or identify available actions to take (actionability). The Patient Education Materials Assessment Tool (PEMAT) is a valid and reliable method to measure the understandability and actionability of online patient education materials. The purpose of this study was to utilize these validated measures to evaluate osteosarcoma online resources for readability, understandability, and actionability. It was hypothesized that current online resources would score adequately on these objective measures and that these measures would correlate with the order of the listed search results (rank).

Methods: Using the search term "osteosarcoma", two independent online searches (Google.com) were performed. The top 50 search results, including rank order, were recorded. Subsequently, websites were included if their purpose was providing osteosarcoma-related patient education. News articles, non-text material (audiovisual), articles (news/research/industry), and websites unrelated to osteosarcoma were excluded. Readability was quantified utilizing the validated Flesh-Kincaid Grade Level (FKGL) algorithm. This objective measure reports readability scores in terms of the average US school level that is required for a reader to comfortably understand the text. Assessments utilizing the PEMAT-P form were performed by two independent authors. A PEMAT score of 70% or below is considered poorly understandable or poorly actionable. The correlation between a website's average Google search rank (from high to low) and its readability, understandability, and actionability was also determined. Statistical significance was defined as a *p value* <0.05.

Results: Of the 53 unique websites, 37 websites (69.8%) met inclusion criteria. The mean FKGL was 12.0±2.4. No (0%) websites scored ≤6th grade reading level (Figure 1). Mean understandability and actionability scores were 57.2±10.7 and 28.0±22.6. Only 10.8% (n=4) scored with the acceptable threshold (>70%) for understandability. Within the websites that met the threshold, 3 were academic (75%) and 1 was a governmental agency (NIH) (25%). Only 1 website (2.7%) scored above the PEMAT actionability threshold (academic) (Figure 2). While 93.9% scored well in regard to layout and design, only 39.4% of websites used visual aids, and only 38.5% of those specific sites had visual aids that reinforce rather than distract from the content. Additionally, under word choice and style, only 42.4% of websites used common, everyday language and only 57.6% appropriately used and defined medical words. There was no association between readability (p=0.15), understandability (p=0.20) nor actionability (p=0.31) scores and Google rank.

Conclusion: Overall, osteosarcoma online patient educational materials scored poorly with respect to readability, understandability, and actionability. None of the online resources scored at the AMA and NIH recommended reading level. Additionally, only four scored above the threshold to be considered understandable by the general public with 75% of those published by academic institutions. Future efforts by musculoskeletal oncology leaders should be made to improve online resources in order to optimize patient knowledge and facilitate informed decision-making.

Mean Readability score per specific patient informative website. The American Medical Association and National Institutes of Health recommend health information to be written at a 6th grade or lower reading level (orange line). None of the mean readability scores met the recommended reading level.



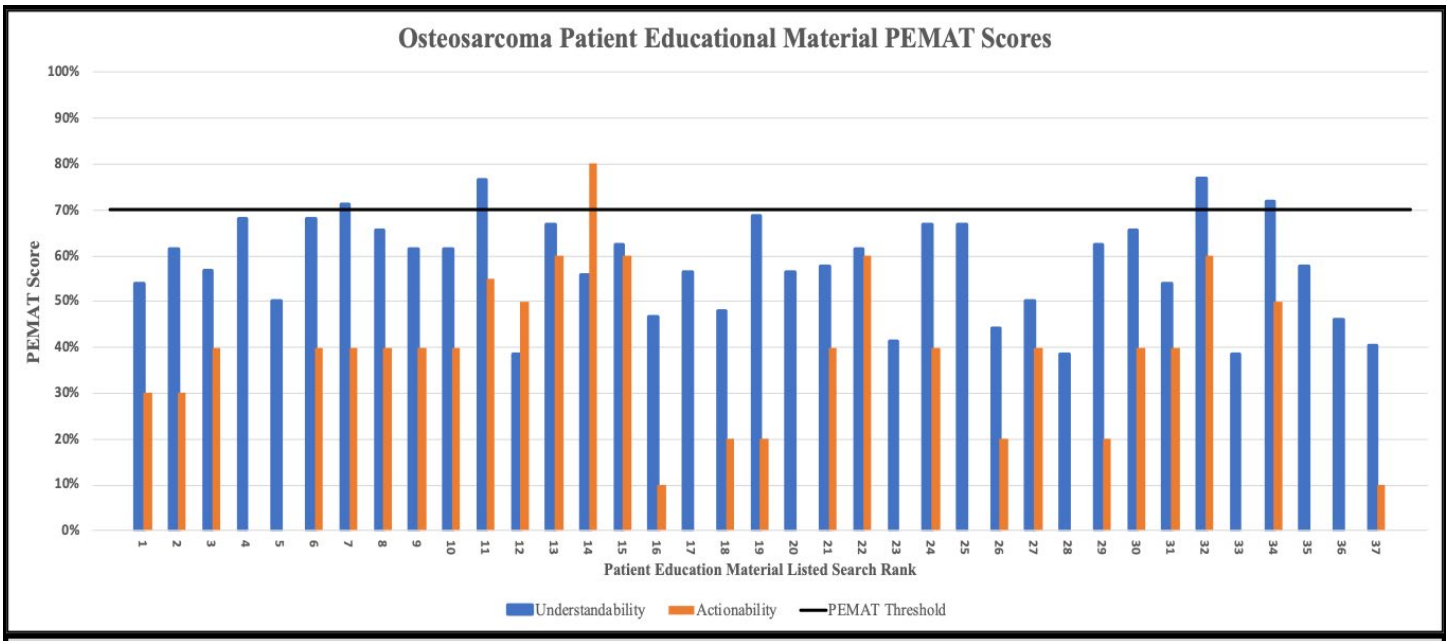


Figure 2: A PEMAT score of 70% or below is considered poorly understandable or actionable. Understandability and Actionability per specific osteosarcoma website in order rank (1-37).

Poster #175 3464247

DEMOGRAPHICS AND OUTCOME OF PATIENTS WITH GYNAE SARCOMA (GS), THE OTTAWA EXPERIENCE

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Objective: The Ottawa Hospital is one of the three Cancer Care Ontario designated Sarcoma Host Sites and one of nine Gynecologic Oncology Centres (GOCs).
Since primary and secondary gynecologic sarcomas are relatively rare and the diagnosis and management is often multi-disciplinary, collaboration between Gynecologic Oncology Centres and Sarcoma Services Host Sites is recommended.

Uterine sarcomas account for approximately 1% of all female genital tract malignancies and 3%-7% of all uterine cancers.
Histologically, uterine sarcomas were classified initially into:
carcinosarcomas (malignant mesodermal mixed tumors), accounting for 50% of cases,
leiomyosarcomas (30%),
endometrial stromal sarcomas (15%),
and undifferentiated sarcomas (5%)

Carcinosarcoma has been reclassified, as a dedifferentiated or metaplastic form of endometrial carcinoma, but is still included in most retrospective studies of uterine sarcomas.
After excluding carcinosarcoma, leiomyosarcoma has become the most common subtype of uterine sarcoma even though it accounts for only 1%-2% of uterine malignancies.
Leiomyosarcomas diagnosed according to the WHO criteria are associated with poor prognosis even when confined to the uterus at the time of diagnosis.

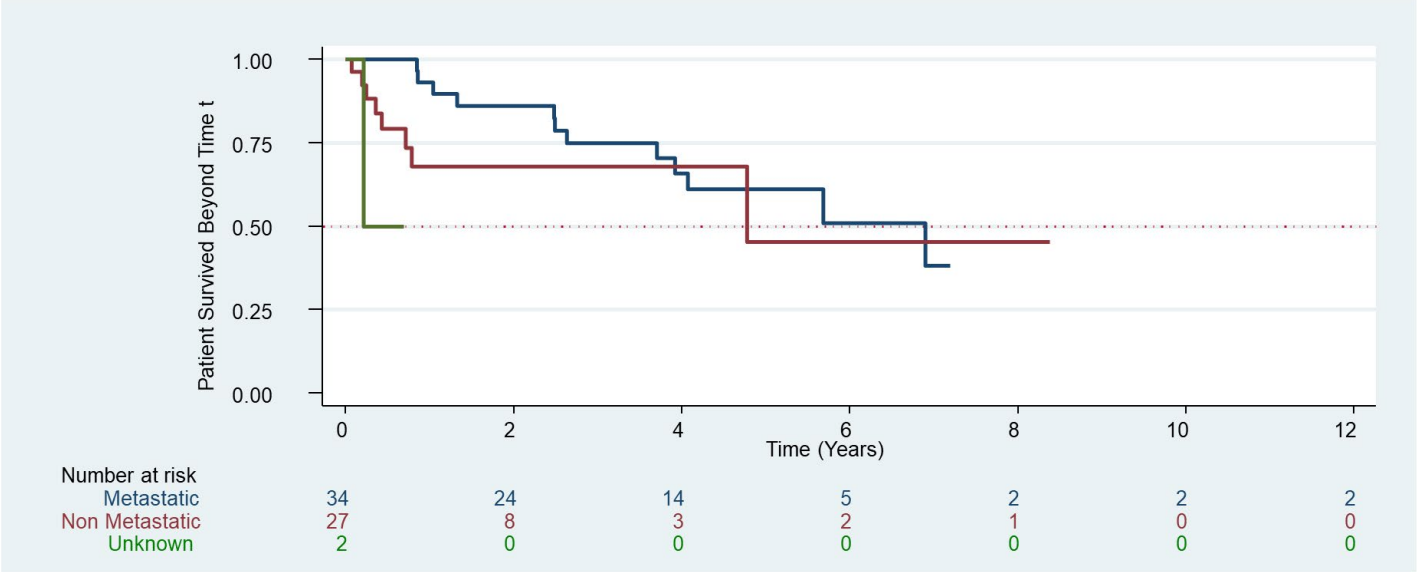
Methods: This study is part of the retrospective sarcoma database project. Ethics approval was obtained. All patients with malignant soft tissue sarcomas of the female organs seen in Ottawa during the period from 2005 to 2014 were captured. All patient's information electronic or otherwise were reviewed. Data collected included patient's demographics, diagnostics and staging information, adverse events and survival by treatment. Data were entered into REDCAP program. Kaplan-Meier analysis for survival and outcome were obtained.

Results: During that period, 63 patients were seen. Median age was 57 years of age and 75% of patients were under 65 years of age. Different histology was seen but 73% of patients were diagnosed with leiomyosarcoma. 54% presented with localized disease but the rest had metastatic disease.
With median follow up for survival of 3.5 years 66% remain alive with median overall survival 5.7 years and 7year actuarial survival of 40%.

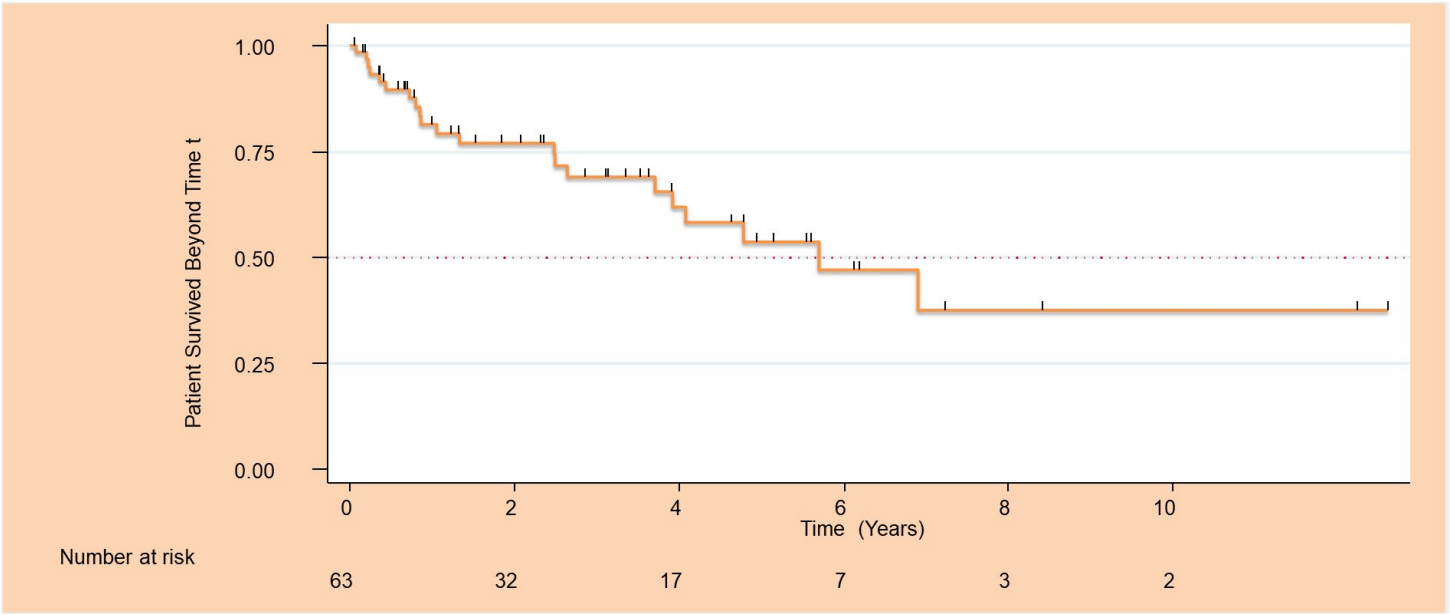
Conclusion: Gynae Soft tissue sarcomas are rare constituting about 5% of all Gynae malignancies. It is perhaps more homogenous than other sites of soft tissue sarcomas. Patient characteristics are consistent with the literature. Overall Survival reflect those reported for earlier stages, although 43 % of patients had advanced disease at presentation.

The mainstay of treatment is surgery with adjuvant radiation treatment commonly used in the post op setting. Distant metastases at presentation is common. Survival remains poor despite improvements in diagnosis, staging and treatment.

Overall Survival by stage



Kaplan Meier overall survival



Poster #176 3464274

MIFAMURTIDE CUMULATIVE DOSE AND PROGNOSIS IN THE ADJUVANT TREATMENT OF PATIENTS WITH NON METASTATIC EXTREMITY HIGH GRADE OSTEOSARCOMA: RESULTS OF THE ITALIAN SARCOMA GROUP (ISG), MULTICENTRIC, PROSPECTIVE, ISG/OS-2 TRIAL

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Objective: Overexpression of ABCB1/P-glycoprotein (Pgp) has been reported as a negative prognostic factor for patients with localized osteosarcoma in retrospective studies. Two prospective trials with Pgp expression as stratification factor were activated in Italy (NCT01459484), and Spain (NCT04383288). Both included the use of mifamurtide added to MAP (methotrexate, adriamycin, cisplatin) regimen in those patients with overexpression of Pgp. Result of ISG/OS-2 trial, were recently presented (ESMO Annual Meeting). We sought to analyze the impact of mifamurtide cumulative dose in the Pgp overexpressing cohort.

Methods: Patients ≤ 40 years with extremity high-grade osteosarcoma were eligible. Pgp expression was centralized. Primary chemotherapy consisted of 2 cycles of MAP. In case of Pgp overexpression, those patients with good response (GR: chemotherapy-induced tumor necrosis ≥ 90%), mifamurtide was added to postoperative MAP. In case of poor response (PR), mifamurtide (2 mg/m2 twice/week for 3 months then weekly for 6 months) was added after surgery, with 4 consecutive cycles of ifosfamide 3 gr/m2/day, day 1-5 (high dose ifosfamide: HDIFO). Effective dose of mifamurtide administered was accounted and Event Fre-Survival (EFS) and Overall survival (OS) were calculated. In order to assess the impact of mifamurtide cumulative dose on prognosis, those patients who stopped mifamurtide treatment due to disease progression were excluded.

Results: From June 2011 to March 2018, 291 ISG patients were included in ISG/OS-2.
154 (53%) of the patients were Pgp+. 3/154 patients did not start mifamurtide for early progression, 8/154 patients interrupting mifamurtide due to progression while on treatment were excluded; this left 143 patients for the present analysis. A GR to induction chemotherapy was reported in 46% of the cases. Full dose (100%) of mifamurtide was given to 77 (54%), while patients 66 (46%) patients received less than 100% of mifamurtide planned total dose.
With a median follow-up of 55 months (range 11.5 – 100.1 months), the 3-year EFS and OS were 74.8% (95% CI 66.6- 81.2) and 92.2% (95% CI 86-95.7). In patients achieving a GR non differences in EFS and OS were observed according to mifamurtide cumulative dose. Among patients with PR, those who completed mifamurtide planned adjuvant course had a better EFS and OS as compared with those who received a shorter mifamurtide treatment. The lack of statistical significance might be related to the relative small number of patients (Table 1).

Conclusion: More than 50% of the patients received the 9-month long schedule of mifamurtide. In GR patients the compliance with mifamurtide treatment does not seem to influence the outcome, whereas in patients with a PR, receiving adjuvant ifosfamide, a worse outcome was reported in case of lower mifamurtide cumulative dose. A pre-planned merged analysis of this study with a twin GEIS observational study is ongoing. This data might inform future trials with mifamurtide.

Table 1. Event-free survival (EFS) and Overall (OS) by muramiltripeptide cumulative dose and necrosis (n=143)

	n	% 3-yrs EFS (95% CI)	p	% 3-yrs OS (95% CI)	p
Necrosis					
GR	66	85.7 (74.3-92.3)	0.0033	100	0.0129
PR	77	65.5 (53.5-75.1)		85.4 (74.6-91.9)	
Muramiltripeptide					
< 100%	66	73 (60-82.4)	0.7160	85.9 (73.8-92.7)	0.3359
100%	77	76.3 (65-84.3)		94.5 (86-97.9)	
Muramiltripeptide in GR (MAP)		73.7 (57.5-84.5)			
< 100%	31	93.5 (76.6-98.3)	0.3002	100%	0.4256
100%	35	79.6 (61.9-89.7)		100%	
Muramiltripeptide in PR (MAP -> HDIFO)					
< 100%	35	54.8 (36-70.2)	0.2426	75.5 (56-87.6)	0.3178
100%	42	73.7 (57.5-84.5)		89.8 (75-96)	

GR: good response; PR: poor response; MAP: methotrexate, adriamycin, cisplatin,; HDIFO: high dose ifosfamide

Poster #177 3464351

PAZOPANIB IN METASTATIC BONE SARCOMAS - A UNICENTRIC RETROSPECTIVE ANALYSIS AT A TERTIARY UNIVERSITY HOSPITAL

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Objective: Pazopanib is an oral, multitargeted tyrosine kinase inhibitor (TKI) against vascular endothelial growth factor receptor-1, -2, and -3, platelet-derived growth factor receptor-α, platelet-derived growth factor receptor-β and c-kit with antiangiogenic and antitumor activity. This drug is approved for the treatment of metastatic soft tissue sarcomas (STS) after chemotherapy. In bone sarcomas, which are rarer than STS, evidence supporting its use is less robust. Recently, a phase 2 single-arm trial evaluated the use of pazopanib in chondrosarcomas. Disease control rate at 16 weeks was 43% (95% CI, 28%-58%). Several retrospective studies also report the use of pazopanib in osteosarcoma patients. In both diseases evidence is lacking and clinical trials including bone sarcomas are needed to better guide optimal therapeutic strategy. Our objective is to analyze the efficacy and safety profile of pazopanib in metastatic or irresectable bone sarcomas, in patients presenting with this diagnosis during a 10-year period at a tertiary university hospital.

Methods: Retrospective unicentric study of patients with diagnosis of metastatic bone sarcoma (i.e., chondrosarcoma, osteosarcoma, Ewing's sarcoma) treated in the last 5 years at a reference center in Lisbon. Data was obtained by reviewing clinical registries of oncology visits.

Results: Five patients diagnosed with metastatic bone sarcoma and treated with pazopanib were identified. Median age at the diagnosis was 44 years old (20-85 years). Histologically, there were two patients with chondrosarcoma and three with osteosarcoma. The cases of osteosarcomas were located in the lower limb and both cases of chondrosarcomas were located in the pelvis. One patient with osteosarcoma and one patient with chondrosarcoma were metastatic at diagnosis, both with multiple pulmonary lesions. The other three patients were submitted to surgery of the primary tumor. Two patients completed adjuvant chemotherapy (EURAMOS protocol) and one was treated with adjuvant radiotherapy. Most tumors presented with a >T1 size (T2 n=1; T3 n=3; 1 missing). Two patients died while still on pazopanib, one patient suspended due to progression and two patients are still on pazopanib with stable disease. The median number of cycles was 14, (1-37 cycles). Progression-free survival (PFS) ranged between 1 and 32 months (median PFS of 10,0 [95%CI, 0,0-31,7]) and median overall survival (OS) was 16,3 months (95%CI, 0,0-50,4). Two patients presented with grade 1-2 hypertension and two patients with gastrointestinal toxicity (grade 1-2: n=1; grade 3-4: n=1).

Conclusion: Pazopanib is a multitargeted oral TKI approved for the treatment of STS. Its use in later lines in metastatic bone sarcomas could be an option but more prospective studies are needed. Patients should be referred to reference centers for optimal treatment, better survival and functional outcomes.

Poster #178 3464362

PROGNOSIS OF PATIENTS WITH GENITO-URINARY SOFT TISSUE SARCOMAS (GUSTS), 10 YEARS EXPERIENCES IN A TERTIARY CARE CANCER CENTRE.

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[1]Radiation Oncology, University of Ottawa, Ottawa, Ontario, CANADA

Objective: The Ottawa Hospital is one of the three Cancer Care Ontario designated Sarcoma Host Sites
Malignant GENITO-URINARY SOFT TISSUE SARCOMAS are rare. Literature are scarce and reported experiences are limited. Here we report a 10 years, population based, teaching centre experience in Ontario, Canada.

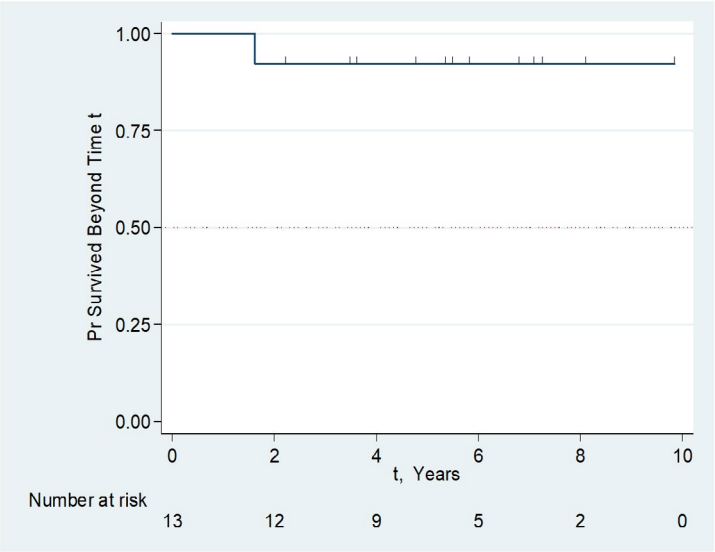
Methods: This study is part of the retrospective sarcoma database project.
Ethics approval was obtained. All patients with malignant soft tissue sarcomas of the genito-urinary tract region seen in Ottawa during the period from 2005 to 2014 were captured. All patient's information electronic or otherwise were reviewed. Data collected included patient's demographics, diagnostics and staging information, adverse events and survival by treatment. Data were entered into REDCAP program. Kaplan-Meier analysis for survival and outcome were obtained.

Results: 13 patients were seen during that period with median age of 55 years and 70 % of the patient being less than 65 years of age. 50% of patients were current or past smokers. Diagnosis was made by needle biopsy in only 2 patients while in the remainder (11 patients) diagnosis was made either by excision biopsy or wide local excision. 5 patients were diagnosed with leiomyosarcomas while the remainder spread over epitheliod, undifferentiated, rhabdomyosarcomas and liposarcomas. 10 patients presented with tumours in the scrotum with 9 being on the left. The majority of tumours were high grade.
In terms of treatment, 4 patients were treated with surgery only, 5 with surgery and chemotherapy, 2 with surgery, radiotherapy and chemotherapy. 2 patients received only palliative treatment.
In terms of pattern of failure, 1 patient presented with nodal recurrence and 3 with distant metastases. At median follow up of 5.5 years, 1 patient died of that disease with actuarial overall survival of 92% at 10 years.

Conclusion: Soft tissue sarcomas of the Genito-Urinary tract are rare but well defined category which seems to carry a relatively good prognosis. Radical surgery remains the main stay of treatment. Early diagnosis could be a factor in the relatively good prognosis.
This study illustrates the value of population based statistics.

A prospective data base is required of all cases diagnosed in Canada

Overall survival



Poster #179 3464399

RADIATION-INDUCED SARCOMA: A RETROSPECTIV POPULATION-BASED STUDY OVER 34 YEARS IN A SINGLE INSTITUTION

Louise Bach Callesen[1], Akmal Safwat[1], Thomas Baad Hansen[2], Flemming Brandt Sørensen[3], Hanne Krog Rose[1], ***Ninna Aggerholm-Pedersen[1]***
[1]Department of Oncology, Aarhus University Hospital, Aarhus, DENMARK; [2]Department of Orthopaedic Surgery, Aarhus University Hospital, Aarhus, DENMARK; [3]Department of Pathology, Aarhus University Hospital, Aarhus, DENMARK

Objective: One of the primary treatment modality of cancer patients is radiotherapy (RT). Because of the carcinogenic effect of ionizing radiation there is a rare riske of developing secondary malignacies including sarcomas. The objective of this retrospective study is to describe the prevalence, patients and tumour characteristics, as well as prognosis and outcome of patients with radiation induced sarcoma (RIS) in a cohort of patients treated in the Sarcoma Centre at Aarhus University Hospital over a period of 34 years.

Methods: All patients, who fulfilled the criteria for RIS and treated in the period 1979 to 2013 were included. The patients' data were retrieved from the Aarhus Sarcoma Registry (ASR) and the National Danish Sarcoma Database (NDSD). the patients were cross-checked with the National Register of Pathology, and validated using the patients' medical records. Descriptive statistics are presented for patients, tumours and treatment characteristics.

Results: A total of 64 out of 2845 patients diagnosed with sarcoma in 1979 until 2013 were diagnosed with RIS corresponding to 2% of all sarcomas. Curatively intended treatment was provided to 45 (70%) patients. The median latent interval from primary malignancy was 11 years (5^{th}-95^{th} percentile: 3-36 years). The most common histologic type was undifferentiated pleomorphic sarcoma (UPS) (33%), followed by angiosarcoma (25%).A total of 50 patients (78%) underwent surgery, of whom 80% had microscopically radical resection (R0). The 5-year OS for the whole cohort was 32% (95%CI: 20-44%). Patients who underwent surgery had a significant better OS compared to patients who were not treated with surgery (Log rank p = 0.002). In the univariate Cox proportional hazard analyses, no metastases at diagnosis, surgery and R0 resection were favourable prognostics factors of survival.

Conclusion: This study showed that RIS patients are unique in their epidemiology and tumour characteristics. They have a poor prognosis and need special research investigating new intensive treatment strategies aimed at improving the outcome.

Poster #180 3464414

FAVORABLE INITIAL TUMOR RESPONSE WITH COMBINATION CABOZANTINIB AND NIVOLUMAB IN STAGE 4 ALVEOLAR SOFT PART SARCOMA

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[2]*Shorewood High School, Shorewood, Wisconsin, UNITED STATES*

Objective: Alveolar Soft Part Sarcoma (ASPS) characterizes a rare and aggressive soft tissue neoplasm. Representing 0.2-1% of all soft tissue sarcomas, ASPS often affects adolescents and young adults. This slow growing, malignant tumor—frequently found in the lungs, brain, neck, and lower extremities—has unclear origin with no standard therapy as it appears to have an intrinsic resistance to chemotherapy and radiation. Cabozantinib (CABO), a c-MET inhibitor, has shown efficacy in phase II trials as has nivolumab (NIVO) in ASPS. Combination of tyrosine kinase inhibitors (TKI) and check point inhibitors (CPI) is being actively studied in many cancers, but very rarely in ASPS. We describe preliminary response in a stage IV, metastatic ASPS young man with combination CABO and NIVO.

Case Report:
A 20-year-old male presented with chronic headaches thought to be migraines. Imaging, however, revealed bilateral enhancing vasogenic lesions suggestive of metastases. Workup showed bulky metastatic disease in lungs, abdomen, pelvis, skull, leg, heart, and vertebrae. Removal of a supratentorial mass showed large packed eosinophilic cells and in alveolar pattern, strongly positive for desmin, TFE3, weakly positive for CD10, Hepar1, and negative for PD-L1, consistent with ASPS. The patient was initially treated with palliative whole brain radiation and dexamethasone, then with oral sunitinib at 3 different institutions. He presented to our clinic 9 months later with 3 large firm, fixed easily palpable masses: skull (4 x 4 cm), parascapular (8 x 6 cm), and thigh (8 x 4 cm). After gaining consent, and armed with the TFE3 staining and ASPL-TFE3 translocation, t(X;17)(p11;q25), known to activate c-MET, we initiated the combination of CABO 60 mg po daily and NIVO 480 mg IV q4 weeks. The patient only received 13 days of daily CABO and 1 dose of NIVO due to febrile neutropenia complicated by rectal abscesses. Physical exam, however, showed the 3 large external masses had dramatically decreased in size. Imaging at start of CABO/NIVO compared to 2 weeks later revealed reduction of parascapular mass [5.3 x 3.1 to 4.3 x 2.2 cm = 27% reduction] and the right hepatic mass [14.7 x 6.8 to 10.0 x 8.6 cm = 14% reduction] with necrosis in both (*Figure 1*).

Methods: We conducted a literature search of PubMed and Google Scholar using keywords: "CPI in ASPS," "TKI in ASPS," "c-MET Inhibitors in ASPS", and "Immunotherapy in ASPS," with clinical trial, meta-analysis, and randomized controlled trial filters applied.

Results: Our search yielded 27 results for ASPS, 8 results for TKI in ASPS, and 3 results for CPI in ASPS. CABO in ASPS yielded one article, NIVO in ASPS yielded zero, and no cases of CABO/NIVO in ASPS were found.

Conclusion: Up to now, both by physical exam and imaging, CABO/NIVO has shown significant reduction in tumor size with associated necrosis in the first 2 weeks. However, our patient did display early toxicity. Now recovered, we have decided to proceed at much lower doses [25% of original dosing] and hope to continue to see objective improvement while limiting toxicity. The optimal treatment for ASPS has yet to be defined. Still, in this hard to treat disease, our patient shows that the combination of CABO/NIVO in ASPS therapy is an attractive treatment option worthy of further study.

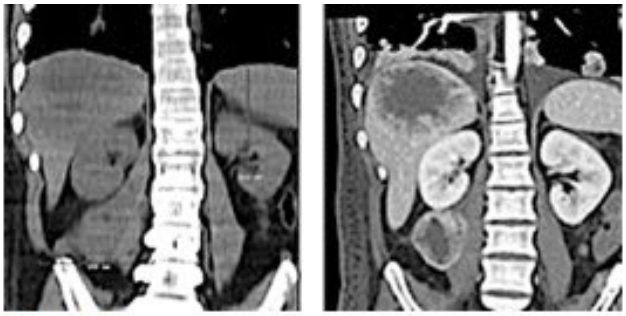

Figure 1. Large right hepatic mass with 14% shrinkage—**14.7 x 6.8** to **10.0 x 8.6 cm**—now with central necrosis. PET-CT scan at initial presentation to our institution (*left*). CT CAP following 2 weeks of CABO/NIVO (*right*) .

Poster #181 3464415

UNDERSTANDING A RARE SUBTYPE: A REVIEW OF 46 PATIENTS WITH GASTROINTESTINAL LEIOMYOSARCOMA TREATED AT A TERTIARY CARE CENTRE

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Objective: Primary leiomyosarcoma (LMS) of the gastrointestinal (GI) tract is rare. Limited literature exists regarding clinical characteristics and outcomes for patients with localised or metastatic disease.

Methods: Retrospective chart review was performed for patients greater than 18 years of age diagnosed with GI LMS on expert pathology review (KT, CF) at The Royal Marsden Hospital between 1 January 2000-1 May 2020. Descriptive statistics were performed. Patients were censored at data cut-off date of 27 June 2020.

Results: 46 patients (Oesophageal n=1, Gastric n=15, Small Bowel n=12, Caecum n=1, Colon n=14, Rectal n=3) with a median age at diagnosis of 54 (range 25-85) were identified. Slightly more patients were male (n=24). Thirteen percent (n=6) of patients had received abdominal radiation therapy for an unrelated cancer.
All of 36 patients with localised disease had resection with oncological margins. One patient received adjuvant chemotherapy and none received adjuvant RT. For patients who underwent potentially curative surgery, median disease-free survival was 14 months. Half of patients (n=18) developed recurrent disease post resection, with the majority distant (n=16) rather than local (n=2). Median overall survival (mOS) was 27 months for patients with distant recurrence. Twenty-one percent (n=10) of patients presented with *de novo* metastatic disease (n by site– 5/10 liver only, 0/10 lung only, 2/10 lung+liver, 3/10 multiple sites). The mOS was 19 months for patients with *de novo* metastatic disease. All patients with metastatic disease and most (n=11/18) with recurrent disease post resection were treated with chemotherapy. Regimens included doxorubicin (n=20) or gemcitabine (n=11) containing, trabectedin (n=12) and other (n=5). Median progression free survival (mPFS) for patients with recurrent disease treated with doxorubicin, gemcitabine and trabectedin was 6.3, 7.4 and 3.4 months respectively compared to 4.3, 2.0 and 8.0 months for patients with *de novo* metastatic disease.

Conclusion: This represents one of the largest reported cohorts of patients with GI LMS. Incidence of prior abdominal radiotherapy was relatively high in this cohort, and its relationship to the development of GI LMS warrants further investigation. We found that the recurrence rate was high and disease-free survival was short even with complete resection. mPFS with chemotherapy was short highlighting the need for improvement in the treatment of metastatic disease.

Poster #182 3464422

POSTERIOR KNEE ARTHROSCOPY FOR PIGMENTED VILLONODULAR SYNOVITIS UTILIZING ULTRASOUND GUIDANCE

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Objective: Entering the posterior knee with arthroscopy can be difficult. Scar tissue, tumor, and the obese patient can make instrument placement difficult and risk neurovascular injury. Pigmented villonodular synovitis (PVNS) can cause a mass effect in the posterior knee, disrupt the location of the normal anatomy, and make visualization inside the joint difficult (Figure 1). Ultrasound can be used in order to visualize the posterior knee and provide direct guidance of instrumentation. We describe the technique for utilizing ultrasound during arthroscopic resection of PVNS from the posterior knee.

Methods: An anterior diagnostic arthroscopy is performed in all cases. The PVNS is resected and a complete synovectomy is performed. In order to perform the posterior arthroscopy, the posterolateral portal is placed first. This allows for minimization of iatrogenic injury to the neurovascular structures which are predominantly lateral. The ultrasound transducer is placed in a sterile cover and visualization of the posterior knee is performed along the short axis. Once the peroneal nerve, popliteal vasculature and the lateral geniculates are identified, the knee is flexed as much as possible while still being able to utilize the ultrasound probe (Figure 2). This allows for the neurovascular structures to move posteriorly and to minimize the risk of iatrogenic injury. A 16 gauge needle is placed under ultrasound guidance into the knee joint. If the distance is short enough, the needle can be placed completely through the joint and through the medial skin in order to place both the lateral and medial portals at the same time. A guidewire is placed through the needle, and the needle is removed. Incisions are made at the skin, and trocars are placed over the needles and into the joint under ultrasound guidance to ensure accurate placement. If the needle is unable to traverse the posterior knee completely, the posterolateral portal is made and a switching stick is then placed through the trocar, across the joint to the posteromedial knee, and an incision is made at the skin where the switching stick is palpated. A trocar is then placed over the switching stick, which is then removed, and the arthroscope and instrumentation are then placed. The saphenous nerve and medial geniculates are visualized with the ultrasound as the posteromedial portal is made to ensure these are not injured.

Results: Seven cases of ultrasound assisted posterior arthroscopy were performed for diffuse PVNS. No patient received any other neoadjuvant or adjuvant treatments. All the patients are without symptoms at most recent follow-up with a range of 2-6 years (Figure 3). Two cases underwent a repeat arthroscopy due to symptomatic recurrence and are currently without symptoms 2 and 4 years after repeat arthroscopic resection. Entry into the posterior compartment was able to be confirmed on ultrasound in all cases. The neurovascular structures were able to be visualized and avoided in all cases.

Conclusion: Ultrasound guidance was found to visualize the neurovascular structures and the knee joint in all cases. This provided for safe placement of instruments as well as the ability to localize the neurovascular structures in relation to the camera and shaver. Ultrasound guidance should be considered during resection of PVNS from the posterior knee.

Figure 1: T1 axial and sagittal MRI of a patient with PVNS of the knee. The arrows demonstrate multiple areas of diffuse, nodular PVNS with erosion of the posterior aspect of the distal femur in close proximity to the popliteal artery and vein.

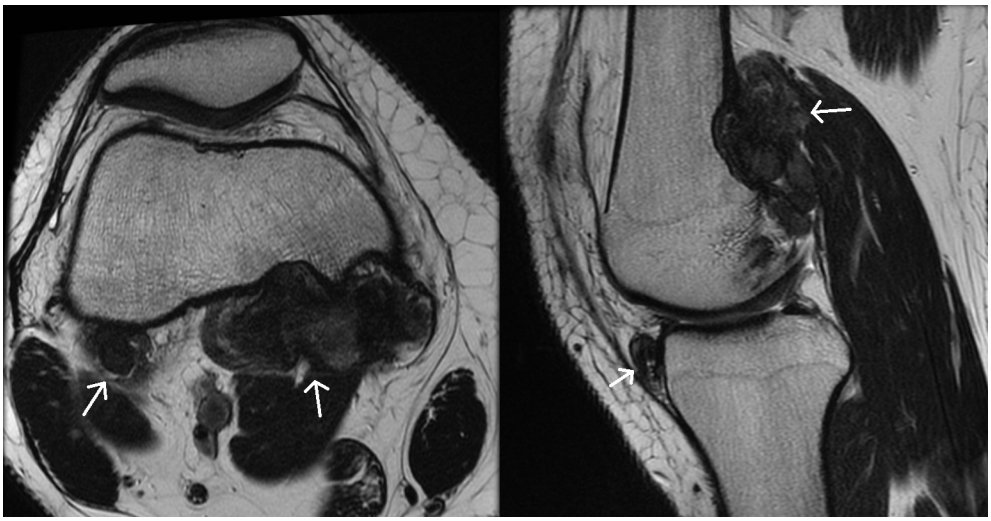


Figure 2: Ultrasound views of a patient with PVNS of the knee. The lateral view on the left demonstrates the anatomic structures and guides safe placement of instrumentation. The medial view shows the anatomic structures in relation to the instrumentation, allowing for safe resection of the tumor.

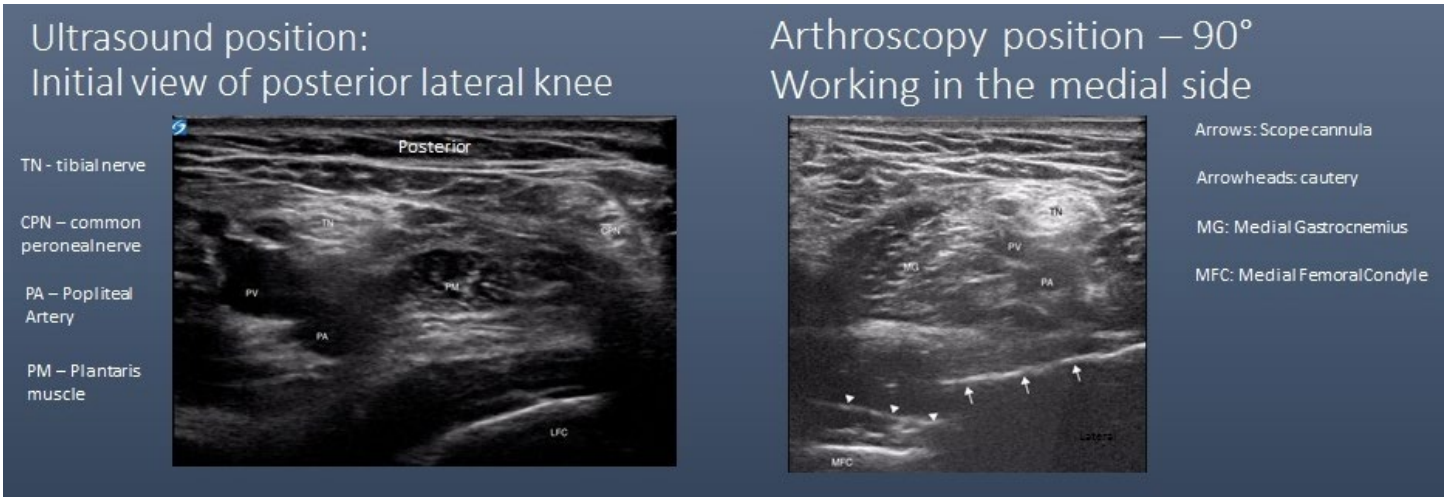
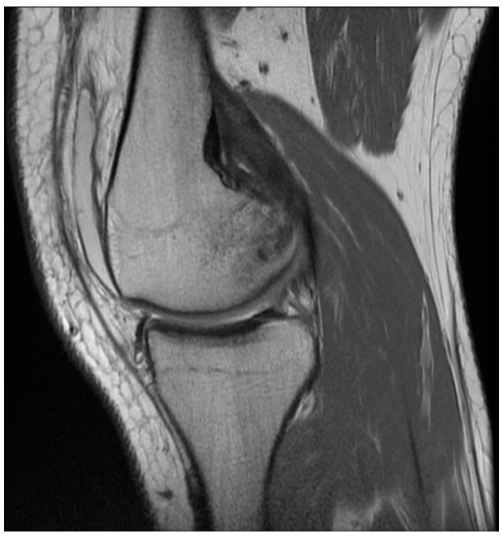


Figure 3: T1 sagittal MRI of a patient with PVNS of the knee initially seen in Figure 1. Two years post-operatively, the patient is asymptomatic and without evidence of recurrence.



Poster #183 3464440

USE OF MAGNETIC GROWING INTRAMEDULLARY NAILS WITH INTERCALARY ALLOGRAFT RECONSTRUCTION AFTER TUMOR RESECTION

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Objective: Reconstruction after excision of tumors has remained challenging. Intercalary allograft reconstruction has remained an option, but is not without complication. Osteosynthesis techniques have included plate fixation, nail fixation, or combined techniques. Non-union occurs more frequently in those fixed with intramedullary nails alone. We previously reported on a novel technique of using magnetic growing intramedullary nails to compress across the entire allograft in 15 osteotomy sites with an 87% union rate. This technique also provides the opportunity to lengthen the bone at a later date using the same implant. The purpose of this study is to evaluate union rates and complications using this technique with a larger sample size and longer term follow-up.

Methods: A retrospective review of 12 patients with 27 osteotomy sites on 7 femurs and 7 humeri was performed. The average age was 45 (9-73) with an average follow-up of 24 months (4-60). Diagnoses included two pleomorphic sarcomas, three osteosarcomas, one metastatic endometrial stromal sarcoma, and six metastatic renal cell carcinomas. Twenty-four osteotomy sites were primary resections, one site was a chronic non-union previously treated with a carbon fiber nail, and two sites were for a revision of a previously fractured intercalary allograft. Five patients received neoadjuvant and adjuvant chemotherapy, and seven patients received only adjuvant chemotherapy. One patient received neoadjuvant radiation. An intercalary allograft with a magnetic growing intramedullary nail was placed. No autograft was used. The average allograft length was 14 cm (5.5-29). The nails were compressed intraoperatively. Radiographs were evaluated to determine union rates, time to union and to evaluate for any graft reabsorption or hardware complications.

Results: Twenty-three out of 27 sites demonstrated evidence of healing after an average of 8 months (4-26) (Figure 1). Complications included 1 fracture through the allograft after a fall, 1 wound dehiscence, an intraoperative fracture of the native bone during surgery in 2 patients and an intraoperative fracture of the allograft in 1 patient. Hardware complications occurred in 6 patients and included the backing out of 4 screws/pegs with one that required removal, fracture of 1 screw, fracture of 1 nail (Figure 2), and cut-out of the nail from the humeral head in 1 patient. Six patients underwent subsequent in-office compression in order to obtain a union. Two patients successfully underwent a total of 3 surgeries for an acquired limb-length discrepancy. There was no evidence of reabsorption of any of the allograft, recurrent tumor, or infections at final follow-up.

Conclusion: In this series, there was a union rate of 79% compared with 87% described previously in 15 osteotomy sites compared to 27 in this report. Intraoperative fractures of the host and allograft bone did not prevent healing of the osteotomy sites. Hardware complications were common and may be improved with the use of a stainless steel version of this nail. No longer term complications such as reabsorption of the allograft, infections or recurrences occurred.

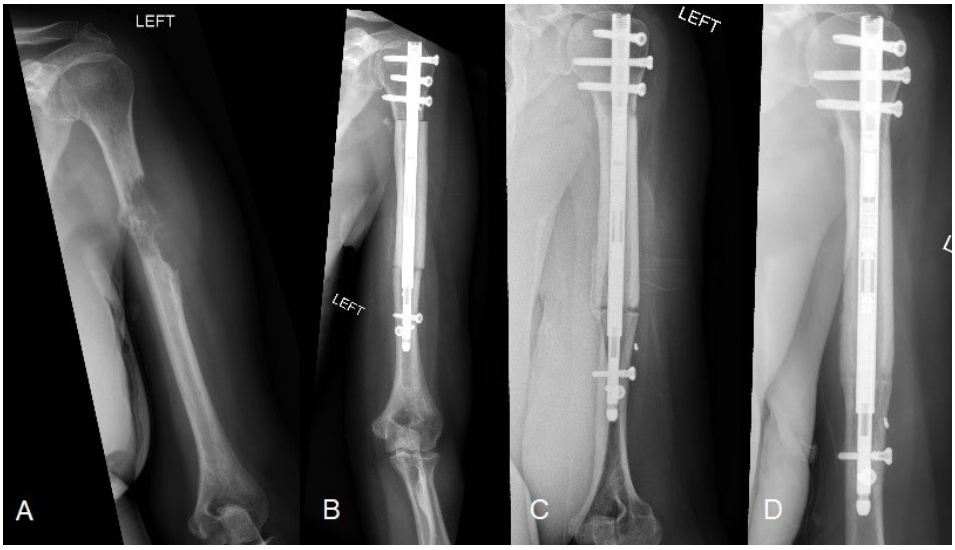

Figure 1: A) 50-year-old female with metastatic renal cell carcinoma to the left humerus with destruction of the bone. B) Immediate post-operative image demonstrating apposition of the allograft to the host bone with the electromagnetic nail in place. C) The proximal osteotomy has healed and early bridging of the distal site is noted. D) Three years post-operatively, healing of both sites is noted with remodeling of the bone and incorporation of the allograft.

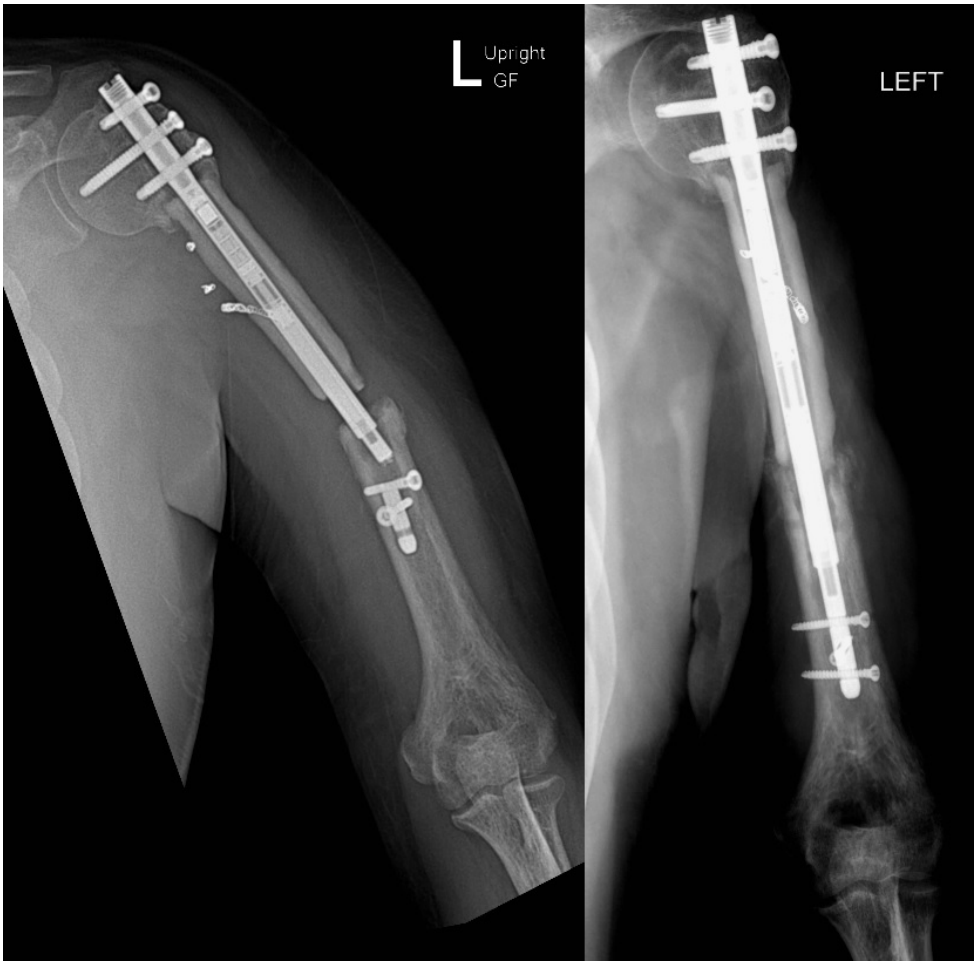

Figure 2: 62-year-old male with renal cell carcinoma who underwent resection of the tumor with placement of an intercalary allograft. The nail has failed at the junction of one of the distal locking screws in the left image. The right image is after revision of the nail. The proximal site was clinically healed during the revision and shows continued remodeling. The distal site is compressed and being followed for evidence of healing.

Poster #184 3464444

ONCOLOGIC INDICATIONS FOR ELECTROMAGNETIC INTRAMEDULLARY NAILS

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Objective: Electromagnetic intramedullary nails have been used extensively in reconstruction for limb-length discrepancies, deformities, and after traumatic injuries. The literature regarding these nails after tumor resection is currently limited to use in allograft reconstruction. Limb-length discrepancies and deformities can commonly occur after tumor resection. This report describes cases where these nails have been used to correct complications that have occurred after tumor resection.

Methods: Three sample cases of reconstruction are presented. One patient had a significant limb length discrepancy secondary to a prior hemipelvectomy (Figure 1). A second patient developed a significant limb-length discrepancy with a valgus and procurvatum deformity of their femur after intercalary allograft reconstruction (Figure 2). The third patient had a "sleeper nail" placed at the time of initial tumor resection as their proximal tibial growth plate was resected and reconstructed with an osteoarticular allograft (Figure 3). They subsequently underwent limb-lengthening after their contralateral growth plate started to close.

Results: The indication for tumor resection included a chondrosarcoma of the pelvis, Ewing's sarcoma of the femur, and osteosarcoma of the tibia. The patients were lengthened 6 cm, 5 cm and 3 cm, respectively. No patient received radiation to the surgical site and the patients with Ewing's sarcoma and osteosarcoma had completed their adjuvant chemotherapy at the time of reconstruction. All patients underwent successful lengthening and two patients had correction of their deformities. The patients currently ambulate without a shoe lift or assistive device. No complications occurred.

Conclusion: Compared to external fixation, electromagnetic intramedullary nails allow for a non-invasive method for the correction of deformities and limb-length discrepancies. Use of these nails can provide a viable solution for correction of these issues that can occur after tumor resection.

Figure 1: 31-year-old female status-post right hemipelvectomy with fusion of the femur to the pubic rami. A) The hip was fused in adduction with some compensation due to a pseudarthrosis of the rami. B) A corrective osteotomy of the proximal femur was performed and lengthening of the femur was started. C) Good regenerate is noted at the osteotomy site during lengthening. D) After the regenerate consolidated, the nail was removed. E) Limb-length radiographs with the pre-operative films on the left and post-operative films on the right demonstrating correction of the adduction and equal leg lengths.

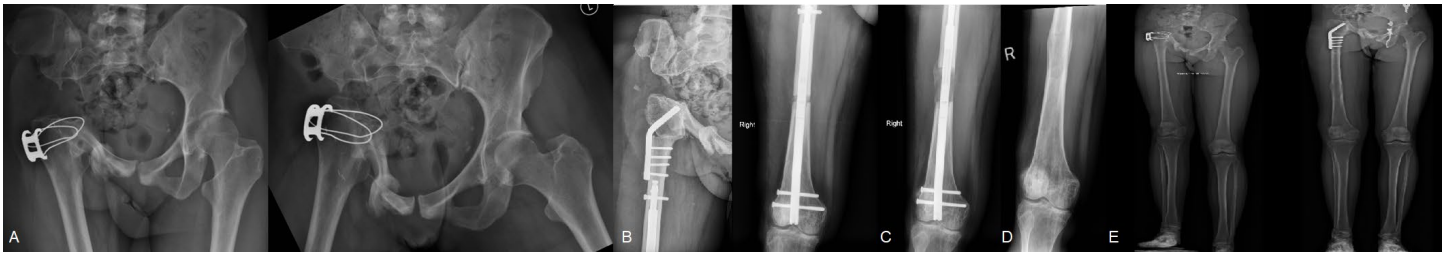


Figure 2: A) X-rays of a 13-year-old female with Ewing's sarcoma of the femur. B) The patient had undergone a prior intercalary allograft reconstruction with overgrowth of the medial growth plate of the distal femur compared to the lateral resulting in a limb-length discrepancy with a valgus and procurvatum deformity. C) An osteotomy was performed distal to the allograft to correct the deformity and D) lengthening was started. E) Limb-length radiographs demonstrating the pre-operative limb-length discrepancy and deformity with subsequent correction of the deformity while undergoing transport. F) The regenerate has consolidated with correction of the limb-length discrepancy and deformity.

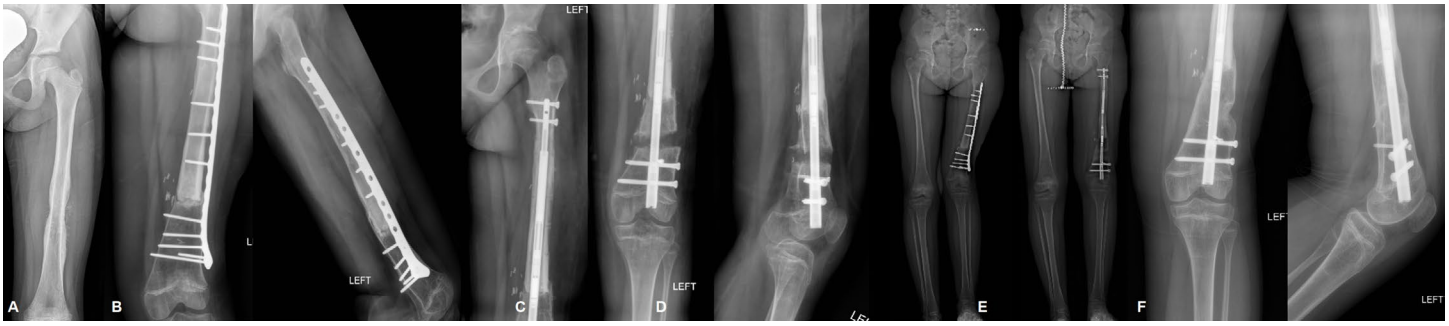
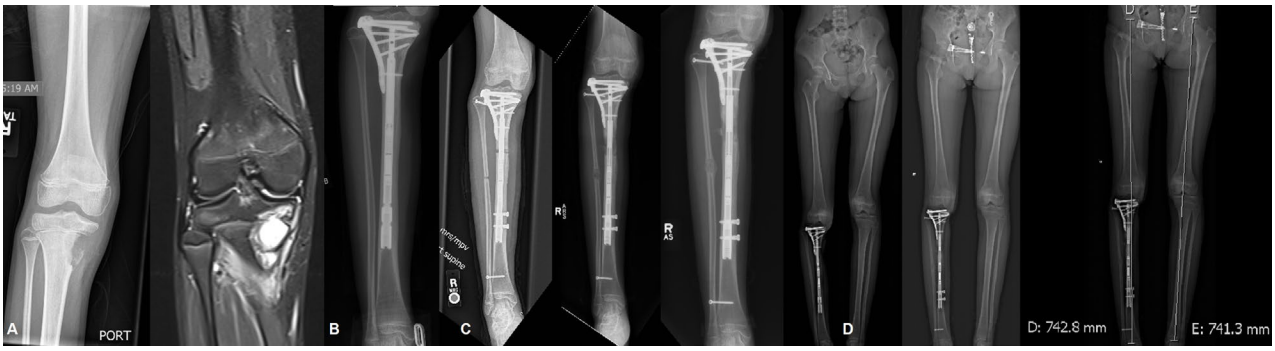


Figure 3: A) X-rays and MRI of a 9-year-old female with an osteosarcoma of the proximal tibia that involved the epiphysis. B) A "sleeper nail" was placed during osteoarticular allograft reconstruction in anticipation of an acquired limb-length discrepancy. C) At 13-years of age, x-rays performed during transport show progressive lengthening and consolidation of the regenerated. D) Limb-length radiographs demonstrating the pre-operative limb-length discrepancy on the left with post-lengthening films on the right. The far-right image shows that the patient's leg-lengths are within 1.5 mm of each other.



Poster #185 3464465

SUPPORTING CLINICAL DECISION-MAKING FOR PI3K/AKT/MTOR INHIBITORS FOR HIGH-RISK PAEDIATRIC AND AYA SARCOMA

Emmy D. Fleuren[1], *Emmy Dolman*[1], *Loretta Lau*[1], *Jinhan Xie*[1], *Daniel Batey*[1], *Chelsea Mayoh*[1], *Paulette Barahona*[1], *Alexandra Sherstyuk*[1], *Dong Anh Khuong Quang*[2], *Marie Wong*[1], *ZERO Preclinical Drug Testing Team*[1], *ZERO Omics Team*[1], *David Thomas*[3], *Emily Mould*[1], *Murray Norris*[1], *Michelle Haber*[1], *Toby Trahair*[1], *Glenn Marshall*[1], *David Ziegler*[1], *Vanessa Tyrrell*[1], *Mark Cowley*[1], *Richard Lock*[1], *Paul G. Ekert*[1]
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Objective: There is an unmet need to identify targeted treatment approaches for young, high-risk sarcoma patients. Aberrations in the PI3K/AKT/mTOR signalling pathway have been reported in various sarcoma subtypes, and targeting its three major nodes (PI3K, AKT, and mTOR) represents an attractive therapeutic opportunity. mTOR inhibitors are of most clinical interest because their side-effect profiles are tolerable, but when used alone or in combination with other agents, have had limited efficacy in childhood sarcoma. As PI3K, AKT and mTOR inhibitors have distinct activities, an important challenge is to identify which sarcoma patients would benefit most from which PI3K/AKT/mTOR-targeted drug.

Our objective is to generate molecular biomarker-driven data in primary patient-derived sarcoma cell models on efficacy of a panel of PI3K-, AKT-, dual PI3K/AKT- and mTOR-inhibitors, to guide clinical trial design and clinical decision making.

Methods: We profiled the PI3K/AKT/mTOR and other kinase signalling pathways of 70 sarcoma patients enrolled in the multicentre prospective ZERO Childhood Cancer precision medicine program, which combines molecular genomic (WGS (tumour, germline DNA)), transcriptomic (whole transcriptome (RNASeq)), and when available epigenomic (methylation) analyses. These profiles were linked to high-throughput (HTS) 3D *in vitro* and combinatorial *in vivo* drug efficacy data for individual patients, where we clustered responders from non-responders. Early clinical response data is taken into account as well.

Results: Fourteen reportable molecular PI3K/AKT/mTOR pathway aberrations were identified in 16% (11/70) of sarcoma patients, affecting PTEN, PIK3CA, PIK3R1, PIK3R2, AKT1, AKT2 and TSC2 genes. Affected sarcoma subtypes include osteosarcoma (OS; 44% (4/9)), Malignant Peripheral Nerve Sheet Tumor (MPNST; 40% (2/5)), embryonal rhabdomyosarcoma (eRMS; 33% (2/6)), alveolar RMS (aRMS; 8% (2/11)), and Ewing sarcoma (ES; 5% (1/19)) patients. HTS drug screening data revealed sensitivity (IC50<1uM) to at least one PI3K/AKT/mTOR-targeted compound in 7/15 screened primary sarcoma patient cultures. Multiple PI3K/AKT/mTOR drug hits were observed in 4 of these patients *in vitro*, of which one harboured a known response marker: a PIK3CA mutation (ES patient). Interestingly, the three other patients, 2 aRMS and 1 OS (all PIK3a- and AKT-inhibitor sensitivity; IC50 values lower than PIK3CA-mutant ES patient), harboured no known molecular PI3K/AKT/mTOR response biomarker. Intriguingly, one of those aRMS tumors was *in vivo* significantly more sensitive to a PI3K-inhibitor monotherapy compared to an mTOR- or AKT-inhibitor, even when mTOR inhibition was combined with chemotherapy. Early clinical data support our preclinical findings.

Conclusion: Using our unique primary, patient-derived sarcoma models we provide the first clues towards differential activity of PI3K/AKT/mTOR-inhibitors across different sarcoma subtypes with various molecular aberrations that could help guide personalised patient treatments. Detailed analysis regarding unexplained drug responses is ongoing.

Poster #186 3464494

ADJUVANT PALBOCICLIB FOR THE PREVENTION OF LOCAL RECURRENCE IN RESECTED LIPOSARCOMA

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Objective: Retroperitoneal liposarcomas are locally aggressive and frequently recur following complete surgical resection. Palbociclib, a CDK4/CDK6 inhibitor, is effective in the treatment of metastatic or unresectable liposarcoma. The use of palbociclib in the adjuvant setting for patients with high risk of recurrence has been described. This study aimed to assess the efficacy of adjuvant palbociclib, compared to post-operative observation, in preventing post-operative recurrence as measured by the time from surgery to either reoperation or use of other systemic chemotherapy.

Methods: Patients with retroperitoneal liposarcoma who received adjuvant palbociclib for prevention of post-operative recurrence were identified from a prospectively maintained institutional database and compared to those who underwent surgery followed by observation alone. We began using adjuvant palbociclib for recurrence prevention in 2017 for patients at high risk of recurrence. Patients were excluded if they underwent surgery prior to 2010 or if they received palbociclib to treat recurrent disease. Patients were defined as undergoing observation if they had an interval of at least 90 days between surgery and adjuvant therapy. Our study's primary outcome, treatment interval, was defined as the time between surgical resection and either re-resection or systemic therapy (other than palbociclib when for recurrence prevention). Clinical and pathological variables were compared using Student's t-test or Fisher's exact test, and differences in the treatment interval were calculated using Kaplan-Meyer methods.

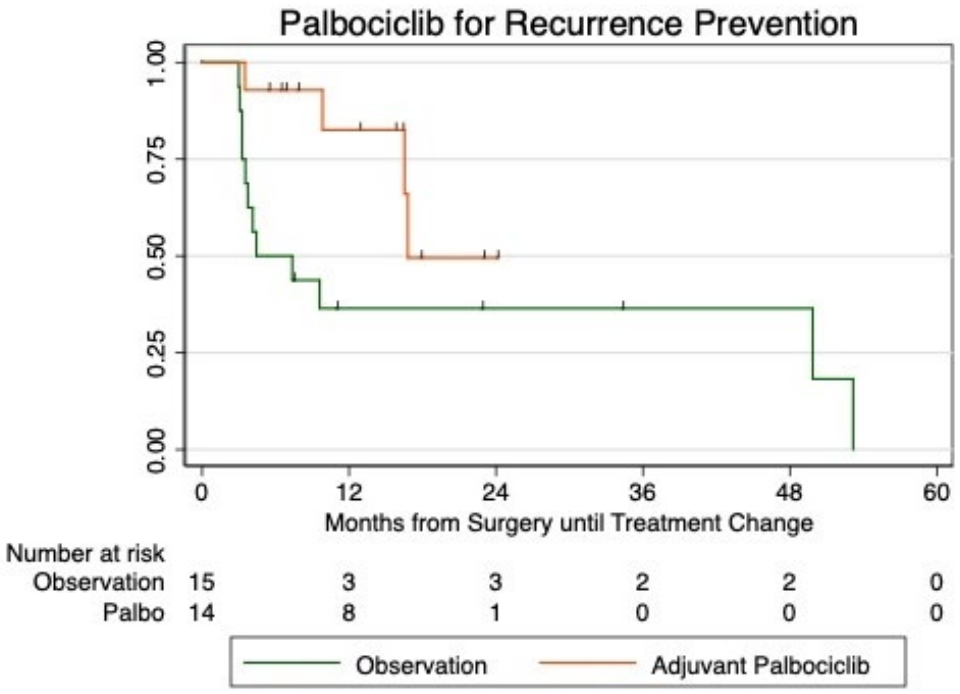
Results: Since 2017, 14 patients have received adjuvant palbociclib for recurrence prevention. They were compared to 15 patients since 2010 who were observed post-operatively without surgery. Histology was primarily dedifferentiated liposarcoma for both groups (observation: 73% (11/15), AP: 71% (10/14). Neither median age (observation: 68.9, IQR: 62.7 - 70.5; palbociclib: 61.1 IQR: 56.0 - 71.5), frequency of R0/R1 resection (observation: 47%, palbociclib: 57%) median tumor size (observation: 12.8cm, IQR 11.4 – 22.2; palbociclib: 21.2cm, IQR: 16 – 25) or performance status differed significantly between groups. Adjuvant palbociclib, for recurrence prevention, was associated with a significantly longer treatment interval that observation alone ($p = 0.03$, log-rank). The median treatment interval was 4.4 months in the observation group and 16.8 months in those receiving adjuvant palbociclib.

Conclusion: Compared to observation alone, adjuvant palbociclib is associated with a prolonged interval between liposarcoma resection and the need for re-resection or other systemic therapy. Palbociclib may be effective at preventing liposarcoma recurrence and its use for this indication warrants prospective study.

Patient characteristics

	Observation (N=15; 52%)	Adjuvant Palbociclib (N=14; 48%)	p-value
Age at Surgery	68.9 (62.7, 70.6)	61.1 (56.0, 71.5)	0.4
Size of Tumor (cm) (N=19)	12.8 (11.4, 22.2)	21.2 (16.0, 25.0)	0.3
R0/R1 Resection	7 (47%)	8 (57%)	0.7
Performance Status (N=28)			
0	4 (27%)	9 (69%)	0.11
1	7 (47%)	4 (31%)	
2	2 (13%)	0 (0%)	
3	2 (13%)	0 (0%)	
Number of Previous Surgeries (N=18)			
0	1 (8.3%)	2 (14%)	0.10
1	5 (42%)	11 (79%)	
2	3 (25%)	0 (0%)	
>2	3 (25%)	1 (7.1%)	
Histologic type			
WD LPS	4 (26%)	4 (29%)	1
DD LPS	11 (73%)	10 (71%)	
Histology Grade (N=27)			
1	4 (29%)	4 (29%)	0.2
2	6 (43%)	5 (36%)	
3	3 (21%)	5 (36%)	

Continuous variables are expressed as median (IQR). Categorical variables are expressed as N (%)



Poster #187 3464514

EARLY DIAGNOSIS OF UTERINE SARCOMA IS ASSOCIATED WITH GRAVIDITY, PARITY, AND HISPANIC ETHNICITY

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Objective: To study the association of the different risk factors and the development of an advanced stage or high-grade uterine sarcoma.

Methods: The Data base of Sylvester Comprehensive Cancer Center and University of Miami Hospital was searched for patients with uterine sarcoma including leiomyosarcoma, rhabdomyosarcoma, Mullerian mixed tumor (carcinosarcoma), and endometrial stromal sarcoma including low grade, high grade and not otherwise specified stromal sarcoma. A total of 175 cases were identified. Data pertaining to possible risk and prognostic factors was collected, this included race, ethnicity, family history of cancer, weight, Body Mass Index (BMI), use of oral contraception (OCP) or hormone replacement therapy (HRT), gravidity, parity, tobacco use, alcohol consumption and diabetes. Descriptive and Analytic statistics were performed using SPSS 25.

Results: Of the 175 cases, 125 cases i.e 71.4% were Caucasian. The mean age at diagnosis was 58.15 years with a minimum of 15 and maximum of 91 years old. The median Seer summary stage and Grade at Diagnosis were 3 and 4, respectively. The mean tumor size was 96 mm (ranging 8 - 340 mm).
Comparing the stage, grade and age at diagnosis among the different groups revealed the mean age at diagnosis was significantly lower in Hispanic compared to Non-hispanic ethnicity with a mean of 53.83 compared to 59.91 (p=0.008). Interestingly, diabetes was associated with a higher mean age at diagnosis, 63.5 years compared to 56.95 years in non-diabetics (p=0.016). A significantly positive correlation was found between gravidity and parity, and the age at diagnosis, r = 0.228 and 0.368 respectively (*p*=0.024 and 0.000).
There was no significant difference among the ethnic groups in regard to the different sarcoma types ($X^2 = 16.567$, *p* value 0.183). Similarly, no significant difference was noted between the sarcoma histologic type among the smoking, alcohol use, family history, OCP/HRT use, or diabetes groups.
Studying the effect of OCP or HRT use on the age at diagnosis did not show a significant difference among the 2 groups (t = -.193, p = 0.848). There was a trend toward a large association between OCP/HRT use and tumor stage ($X^2 = 8.122$, $p = 0.322$). Similarly. OCP were not significantly associated with the grade of the sarcoma ($X^2 = 2.8$, $p = 0.833$).

Conclusion: Our data show that uterine sarcomas tend to occur more commonly in white females. It occurs in Hispanic females at a younger age compared to non-Hispanic females. Ethnicity, diabetes, Gravidity and Parity were associated with significant difference in the age at diagnosis. Some of these can be considered as protective associations while others are considered possibly harmful.
None of the other possible risk factors were significantly associated with either tumor grade, stage, or age at diagnosis.

Thought for the future:
Further studies are needed to delineate the causality among these risk factors and the development of uterine sarcoma. The study of the association between the different factors and survival would help evaluate their prognostic potential and possibly develop a new wholistic scoring system that separate low risk from high risk patients.

Association of the mean age of diagnosis with smoking, alcohol intake, ethnicity, diabetes, family history of cancer and prior use of OCP or HRT

Mean age at diagnosis				
	A	B	Statistics	ρ value
Smoking A: smokers B: non-smokers	61.76	57.19	t = 1.87	0.63
Alcohol A: history of or current alcohol use B: Never used Alcohol	56.57	59.07	t = -1.1	0.271
Ethnicity A: Hispanic B: Non-Hispanic	53.83	59.91	t = -2.66	0.008
Diabetes A: Diabetic B: non-diabetic	63.5	56.95	t = -2.42	0.016
Family history A: positive family history of cancer B: no Family history of cancer	59.61	55.82	t = -1.67	0.96
Use of OCP, IUD or HRT A: Prior use B: never use	60.63	60.08	t = -.193	0.848

t independent sample T-test

Correlation of Age of diagnosis, Stage and Grade with BMI, Weight, Tumor size, Gravidity and Parity.

	Age at Diagnosis		Stage		Grade	
	Statistics	ρ value	Statistics	ρ value	Statistics	ρ value
Weight	r = -0.006	0.946	r = 0.031	0.723	r = 0.010	0.912
BMI	r = 0.017	0.835	r = 0.032	0.710	r = 0.068	0.427
Tumor size	r = -0.244	0.004	r = -0.137	0.126	r = -0.081	0.368
Gravidity	rs = 0.228	0.024	rs = -0.016	0.884	rs = -0.026	0.817
Parity	rs = 0.368	< 0.001	rs = 0.099	0.361	rs = -0.011	0.923

r Pearson Correlation
rs Spearman's Rho

Poster #188 3464550

TRANSFORMED CANINE AND MURINE MESENCHYMAL STEM CELLS AS A MODEL FOR HIGH GRADE SARCOMA WITH COMPLEX GENOMICS

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Objective: Sarcomas are rare mesenchymal tumours with a broad histological spectrum, that can be divided in two groups based on molecular pathology: sarcomas with simple or complex genomics. Tumours with complex genomics are often high grade and have a myriad of genomic alterations, such as aneuploidy and copy number gains and losses, which hampers the detection of early, initiating events in tumorigenesis. As often no benign precursors are known, good models are essential. In this study, we aimed to identify driver events for high grade sarcomas with complex genomics.

Methods: Bone-marrow derived murine (n=6) and canine (n=6) mesenchymal stem cells (MSCs) were isolated and cultured long-term. MSCs were characterized by trilineage differentiation. Transformation of MSCs occurred after long-term culture and was assessed *in vitro* by karyotyping and soft-agar anchorage independent growth assay. To confirm transformation and tumorigenicity of transformed MSCs *in vivo*, we injected murine (n=3) and canine MSCs (n=1) subcutaneously into BALB/c nu/nu mice. Using whole genome sequencing, we compared genomes of non-transformed and transformed canine and murine MSCs to identify drivers of transformation. We used an *in vitro* KO of exon 2-10 of *Trp53* in murine MSCs to observe whether this affected transformation in MSCs.

Results: After long-term culture all murine MSCs and one canine MSC culture spontaneously transformed. Whereas non-transformed MSCs showed normal osteogenic and adipogenic differentiation capacity, only 2 out 7 transformed MSCs retained their differentiation capacity after transformation. All transformed MSCs showed an abnormal karyotype, but only 3 out of 7 MSC cultures were able to form colonies in a soft-agar anchorage independent growth assay. However, *in vivo* all transformed murine MSCs, and not canine MSCs, were able to form tumours after subcutaneous injection into mice. The morphology of these tumours was variable, either resembling human osteosarcoma, with production of osteoid by highly pleomorphic tumor cells, or resembling undifferentiated (pleomorphic) sarcoma. Whole genome sequencing revealed that spontaneously transformed murine and canine MSCs show a complex karyotype with aneuploidy, point mutations, structural variants, inter-chromosomal translocations and copy number gains and losses. Cross-species analysis revealed that point mutations in *Tp53/Trp53* are common in transformed murine and canine MSCs. Murine MSCs with a cre-recombinase induced deletion of exon 2-10 of *Trp53*, transformed earlier compared to WT murine MSCs.

Conclusion: Our model shows that transformed murine and canine MSCs can be used to identify genes involved in transformation towards high grade sarcoma with complex genomics, and confirms the crucial role of p53 in this transformation process.

Poster #189 3464563

PATIENT ADVOCATES TRANSFORMING SARCOMA CARE IN INDIA

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Objective: In India health care related issues and infringemnt of patient's rights are on an increase. Primary aim is to identify how Patient Advocates help bridge the gap between patient and Health care providers to improve or maintain high quality health care for patients.

COMPLETE PATIENT LIFE CYCLE MANAGEMENT:
IMPROVE OVERALL QUALITY OF HEALTH CARE BY SUPPORTING PATIENTS AND THEIR FAMILIES

To promote awareness of Sarcoma among all sections of the Indian people.
Build companionship with sarcoma affected families and strengthening them.
Make difference in sarcoma care in India.
Sensitizing people to not ignore early symptoms and get treated in time for a cure.
Assisting patients in timely detection like biopsy and imaging and advising them the best course of action.
Assisting patients in various diagnostic tests.
Assist the patients in the various treatment planned like surgery radiotherapy, chemotherapy.
Helping improve quality of life of people living with sarcoma.
Assisting patients to adjust to the new normal on completion of treatment.
Assisting patients to re-embark on their professional life.
Assisting patients to complete their education or any other dreams left midway.

Methods: Listing various activities by Patient Advocate Groups both inside Health Care Services and support offered outside Health Care Services
Relevant Data to support the activities
Survey in the form of objective questionnaires to asses the improvement in quality of patient life cycle management.
SWOT Analysis, (Strengths, Weaknesses,Opportunities and Threats) on working of patient advocate groups to measure their work criteria.
Build strong network of individuals who will work towards the objective
Share knowledge about sarcoma with patients and their families
Guide patients for getting required diagnostic tests and timely detection
Guide patients on treatment for surgery, radiation, chemotherapy
Provide psycho social support to patients and their families
Counseling at various levels specially to counter side effects of treatments like Chemotherapy and Radiotherapy
Help patients and care givers understand the disease and various treatment possibilities
Provide required administrative and logistic support to patients and their families
Provide possible financial support for treatment or medicines
Creating rehabilitation support for patients and survivors
Transmitting, printing, circulating, distributing relevant information and knowledge to patients and their families through books, pamphlets, notices, pictures, periodicals, newspapers, magazines or any other mode related to sarcoma
Use of social media and audio visual presentations for furtherance of sarcoma care awareness
Organizing meetings and workshops or seminars of expert health care professionals and patients and their families
Approaching various Corporate Houses, Govt Agencies, High Net Worth individuals and Pubic at large for their involvement and financial support
*Please Refer Image Attached

Results: Successfully bridging the gap between health care facilities and the unmet needs of the patients and the families during treatment
Successfully assisting the patient and their families in navigating the various line of treatments
Successfully improving the overall quality of health care systems in India

Conclusion: Immense success due to community awareness programs led to general public participation which in turn led to early detection of cancer. leading to proper assessment and consultation at appropriate facilities and patients could be treated in time. Advocacy groups play a very important role in getting various govt grants and other facilities and also other support groups were roped in to help. Thus higher success rate of treatments were seen in the patients assisted by Patient Advocate groups. A clear indication that not only more patient advocate groups are needed to strengthen health care in India but also that the existing Patient Advocate Groups be supported and strengthened by involving them in the day to day working of health care facilities.

Poster #190 3464611

CHARACTERIZING THE EFFICACY OF IMMUNE CHECKPOINT INHIBITOR-BASED TREATMENT IN SELECTIVE SUBTYPES OF ADVANCED SARCOMA PATIENTS

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Objective: In recent years, immune checkpoint inhibitors(ICIs) are highly explored for some specific subtypes of sarcoma, such as alveolar soft-part sarcoma (ASPS), undifferentiated pleomorphic sarcoma (UPS). However, their efficacy on other sarcoma subtypes and combination options with anti-angiogenesis TKI and chemotherapy are still not clear.

Methods: We retrospectively analysed 33 advanced sarcoma patients who were treated with PD-1 or PD-L1 inhibitor in our single center from September 2018 to June 2020. Of these, 15 males and 19 females; median age was 45 (range from 34 to 65). Among them, 7 ASPS, 6 UPS, 12 LMS (leiomyosarcoma), 6 DDLPS (dedifferentiated liposarcoma), 2 MFS (myxofibrosarcoma). Treatment regimens are ICI alone or in combination with anti-angiogenesis TKI (such as Anlotinib,Pazopanib) or with chemotherapy. Best change from baseline were assessed by RECIST 1.1 evaluation criteria. mPFS was calculated by Long rank test statistical method.

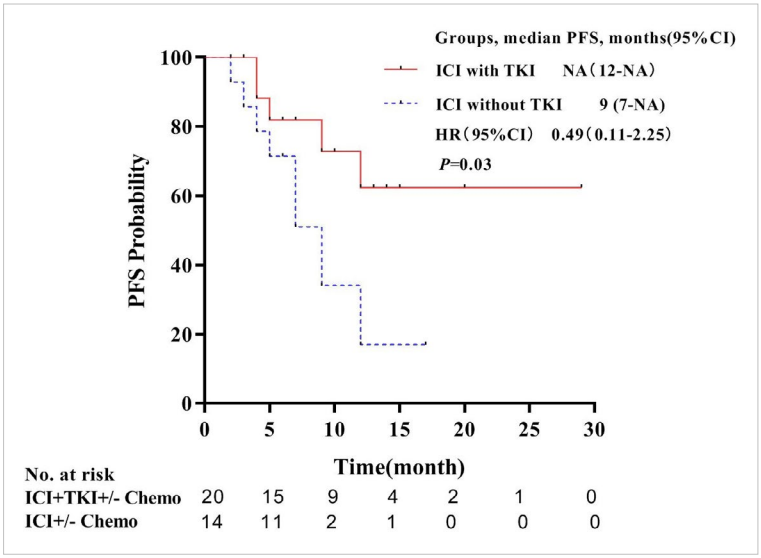
Results: In general, we found that without considering whether concurrently use chemotherapy or not, addition of anti-angiogenic TKI to ICIs significantly prolonged mPFS compared with non-TKI group, the mPFS were NA (95% CI 7-NA) and 9 months (95% CI 12-NA) respectively, 12 month PFS rate increased from 17.0% (95% CI 0.44-0.97) to 65.3% (95% CI 0.03-0.93) (Figure1). The best change rate from baseline in TKI group is higher than that in non-TKI group in general(Figure2). In subgroup analysis (Figure3)(Table 1) , ASPS and UPS were still proven to benefit from immunotherapy most. In ASPS group, 3 patients were treated with single agent PD-1 and 4 patients were treated with PD-1 in combination with anti-angiogenesis TKI. All of the 7 patients had PR or sustained SD. In UPS group, the total DCR was 100%, among whom 4 PR and 2 SD (including 1 SD lasted for 16 months). In DDLPS group, one patient responded 38% tumor shrunk treated with immuno-TKI-chemo combination therapy, 3 patients PD in less than 6 months, 2 patients stayed SD till data cutoff (both less than 6 month). Notebly,both of the two MFS patients performed well from PD-1 combination treatment, 1 PR and 1 SD lasted for 13months PFS. Unfortunately LMS didn't show benefit from immunotherapy, no matter combined with TKI or chemotherapy(Table 1). One LMS patient who achieved pCR after 8 months of immuno-TKI combination treatment followed by tumor resection, stayed 21 months of DFS with no further therapy but close follow-up. We found his gene type is dMMR.

Conclusion: ICIs based treatment may be an effective choice in selective subtypes of advanced sarcoma, such as ASPS, UPS, DDLPS and MFS, especially in combination with Anti-angiogenesis TKI. LMS response less to ICIs, more research are needed to overcome its resistance to treatment.

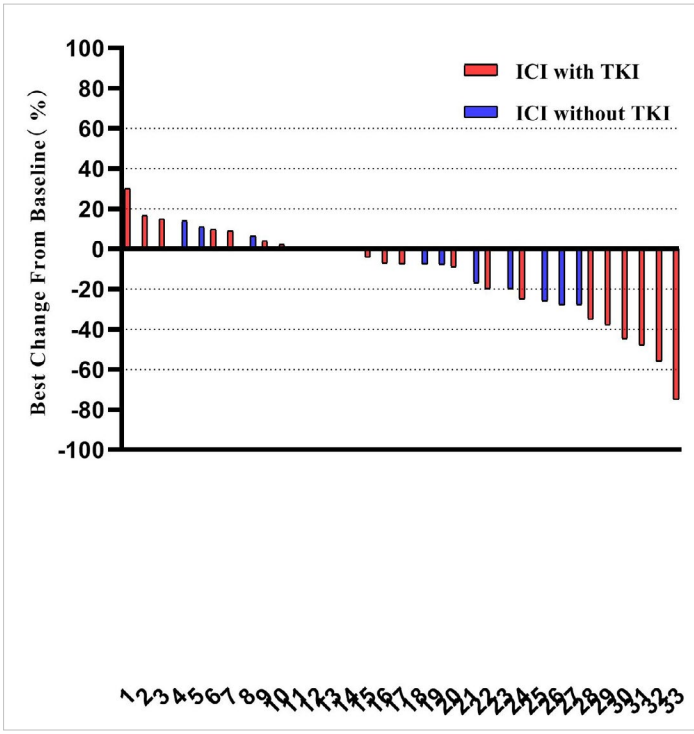
Number of patients who were CR+PR+SD (DCR) undertook different ICI based therapy regimens assessed by best response from baseline in different subtypes.

RECIST Criteria	ASPS(n=7)	UPS(n=6)	DDLPS(n=6)	MFS(n=2)	LMS(n=12)
ICI	3	1	0	0	1
ICI+TKI	4	1	0	1	6
ICI+Chemo	0	3	3	0	2
ICI+TKI+Chemo	0	1	3	1	2

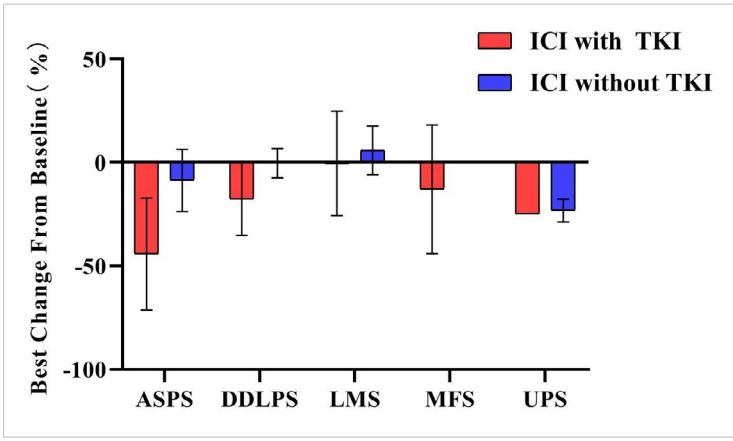
PFS of patients treated by immnotherapy based strategy with or without TKI combination.



Tumor diameter best change from baseline for each case treated by immnotherapy based strategy with or without TKI combination.



Tumor diameter change treated by immnotherapy based strategy with or without TKI combination in different subtypes, each bar shows the average percentage of tumor diameter change from baseline with standard error marked.



Poster #191 3464643

IMMUNE-MATRIX GENE EXPRESSION SIGNATURES OF CYTOKINES, CHEMOKINES, IMMUNE CHECKPOINTS, MATRIX METALLOPROTEINASES AND TISSUE INHIBITORS OF METALLOPROTEINASES IN FORMALIN-FIXED PARAFFIN-EMBEDDED HUMAN CHONDROSARCOMA SAMPLES

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Objective: Conventional chondrosarcoma (Grades 1-3) has no known standard chemotherapy options. The aim of the present study was to define a gene expression profile based on immune response targets analyzing formalin-fixed paraffin-embedded (FFPE) tissue samples from chondrosarcoma patients with potential indication for immunotherapy.

Methods: Forty-one FFPE tissue samples and paired hematoxylin-eosin slides were obtained from resection material of chondrosarcoma patients attended at the Coimbra Hospital and Universitary Centre (Portugal) after the approval of the Hospital Ethics Committee and obtained patient informed consent. Chondrosarcoma patient group consisted of 24 females and 17 males with 58±15 years old (range 25-29). Three sub-groups were established according to histology (Grade 1, n=14; Grade II; n=14; Grade 3, n=13). RNA was extracted after tissue homogenization and subjected to reverse transcription and cDNA synthesis. A gene expression panel of 64 gene specific targets including cytokines, chemokines, immune checkpoints (ICPs), matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) was used for calibrated normalized relative quantification (CNRQ) by real-time quantitative PCR (RT-qPCR).

Results: Twenty-three genes showed statistically significant differences for grade 1, 2 and 3 STS patients [Figure 1]. These targets included genes encoded for cytokines (IFNG and IL10), chemokines (CXCL10/IP10), immune checkpoints (CD274/PD-L1, PDCD1LG2/PD-L2, TNFRSF9/CD137 and IDO1), NK cell receptors (KLRC1/NKG2A and CD226/DNAM-1), matrix metalloproteinases (MMP2, MMP9, MMP12, MMP14, MMP16, MMP19, MMP20, MMP23A, MMP27), tissue inhibitors of metalloproteinases (TIMP1, TIMP2, TIMP4, TIMP4) and fibronectin (FN1).
Clustering of multivariate data using Principal Component Analysis (PCA) and heatmaps [Figure 2] allowed the recognition of 3 clusters of STS samples defined by different levels of matrix-associated genes, immune checkpoints and NK cell receptors.

Conclusion: Gene expression analysis of STS specimens could give functionally relevant information regarding the primary tumor and help to define adjuvant therapy. In this study, we identified different gene expression profiles in a group of STS patients with grades 1 to 3.
Although partially concordant with the histologic grading, these clusters could help to identify patients with unique immune-matrix landscapes.

Figure 1. Gene expression profiling of FFPE Chondrosarcoma samples. Targets of interest with statistically significant differences between grades are shown.

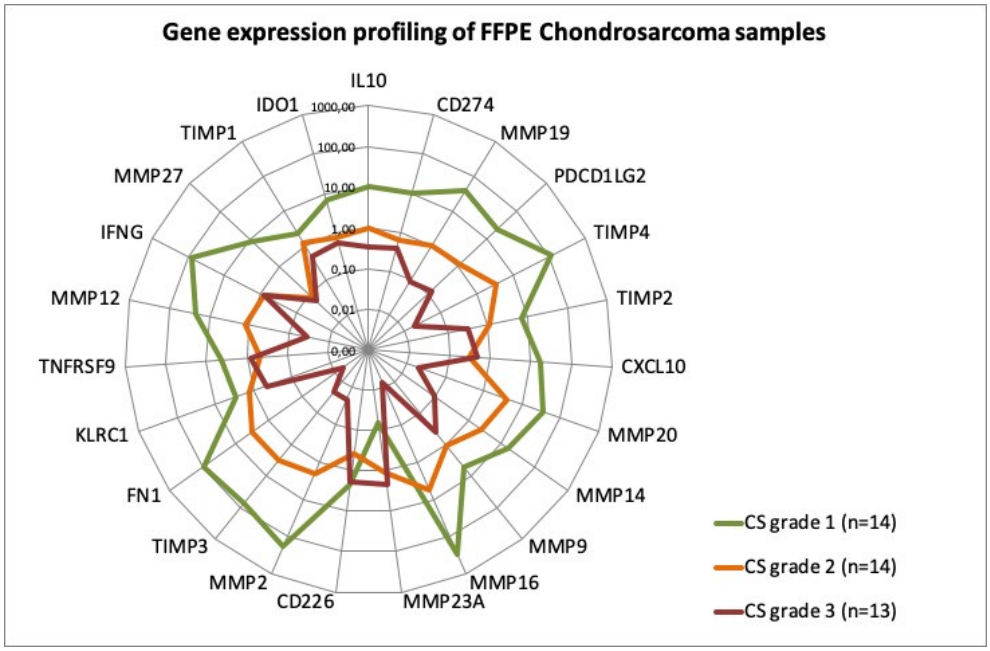

Figure 2. Clustering of multivariate data using Principal Component Analysis (PCA) and heatmaps of calibrated normalized relative quantification (CNRQ) of gene expression in Chondorsarcoma FFPE tissue samples.

Poster #192 3464670

THE MUSCULOSKELETAL TUMOR REGISTRY: LESSONS, BARRIERS, AND FUTURE GOALS

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Objective: In the summer of 2018, the Musculoskeletal Tumor Society and American Academy of Orthopaedic Surgeons (AAOS) began a collaboration to create the Musculoskeletal Tumor Registry (MsTR), a national database of extremity sarcoma. A 6-center pilot trial began to create data collection forms ("smartforms") integrated into the Electronic Health Record (EHR), determine successful strategies for implementation, and identify potential barriers to participation.

Methods: The 6 pilot sites (Iowa, Dartmouth, Johns Hopkins, Ohio State, Cleveland Clinic, Stanford) were chosen because they are major tertiary care hospitals with a large sarcoma service, are led by dedicated orthopaedic oncologists, all use Epic as their EHR, and all were current participants in the American Joint Replacement Registry. The latter two aspects were important to streamline institutional approval and smartform creation. The pilot trial participants joined monthly calls with the information technology and registry administration of the AAOS.

Results: The pilot trial concluded in March of 2020, and the MsTR was approved to officially join the AAOS family of registries. Five of the 6 pilot sites were able to obtain full institutional approval and identify eligible sarcoma patients for inclusion in the registry. The primary concerns included issues regarding patient confidentiality, data ownership, and informed consent. The pilot trial participants agreed on a final data element list that included the necessarily detail to inform a quality and patient safety registry. The patient, tumor, and treatment factors included will allow for future query of clinical research questions.

Conclusion: The pilot trial allowed for anticipation of areas of concern as more institutions are recruited for participation. The Epic smartforms will be used as a template as additional hospitals and EHRs are contracted. The short-terms goals of the MsTR are to increase institutional participation and awareness, and ensure data accuracy and completeness. Longer-term goals include exploring functional and oncologic outcomes after surgical management of extremity sarcoma, and incorporating metastatic disease of bone and spinal sarcoma into the registry.

Poster #193 3464730

PATTERN OF PRESENTATIONS, OUTCOME OF TREATMENT, AND PATTERN OF FAILURE OF PATIENTS WITH GASTROINTESTINAL ADULT SOFT TISSUE SARCOMAS: A 10 YEARS' EXPERIENCE IN A TERTIARY CANCER CENTRE

Dalia Ibrahim[1], *Prudence Buchanan*[1], *Samy El-Sayed*[2]
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Objective: Malignant gastrointestinal soft tissue sarcomas are rare. Literature are scarce and reported experiences are limited. Recent changes in diagnosis and treatment have created a renewed interest in this category. Here we report a teaching center experience in Ontario.

Methods: This study is part of the retrospective sarcoma database project. Ethics approval was obtained. All patients with malignant gastrointestinal soft tissue sarcomas seen in Ottawa during the period from 2005 to 2014 were captured. All patients' information electronic or otherwise were reviewed. Data collected included patients' demographics, diagnostics and staging information, adverse events, and survival by treatment. Data were entered into REDCap program. Kaplan-Meier analysis for survival and outcome were obtained.

Results: 28 patients were seen during that period. Median age at diagnosis was 56 years with 75% of patients less than 66 years of age. Male to female ratio was 2:1. Diagnosis was obtained by needle biopsy in 12, excision biopsy in 6, and wide local resection in 10 patients. 20 patients were diagnosed with gastrointestinal stromal tumours and 8 patients with other soft tissue tumours. At presentation, 50% of the tumours measured less than 5 cm and 25% had evidence of metastatic disease. 19 patients were treated with surgery and 5 patients with surgery and systemic treatment. 4 patients received palliative treatment. Following initial treatment, 5 patients have developed local recurrence. With a median follow up of 4.8 years, 19 patients remain alive with median survival of 8.1 years and 10-year survival of 38%.

Conclusion: Influence of recent change in diagnosis and the innovation of new targeted therapy for this group of patients is demonstrated in the longer survival, despite overall poor prognosis. While the value of systemic therapy is demonstrated in the palliative setting, studies are being carried out to demonstrate its value in the adjuvant setting in the group of patients with gastrointestinal stromal tumours.

Poster #194 3464830

ASSOCIATIONS OF KNOWN SUSCEPTIBILITY LOCI AND GENETIC ANCESTRY ON EWING SARCOMA RISK IN LATINOS

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Objective: Ewing sarcoma (ES) displays dramatic differences in incidence by race, with individuals of European ancestry at highest risk. Evidence suggests that these disparities are influenced by genetic ancestry. Most notably, the binding affinity for EWS-FLI1, the chromosomal translocation pathognomonic for ES, appears polymorphic between individuals of divergent genomic ancestry. Recently, GWAS of ES in Europeans discovered 6 risk alleles. However, it is currently unclear whether these alleles underlie observed racial disparities. In this study, we first sought to replicate the effect of these 6 risk alleles in an independent set of European cases and controls. We then examined whether their effects generalize to Latinos, an admixed population with 2/3 the risk of ES as Europeans. Finally, we evaluated the influence of genomic ancestry on ES risk in Latinos after controlling for known risk alleles.

Methods: ES cases were identified from Project GENESIS (Genetics of Ewing Sarcoma International Study, COG AEPI10N5, supported by 5R01CA161780 and 1X01HL132385-01 from the Gabriella Miller Kids First Program), an international genetic epidemiology study. We identifed Latino controls from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) and European controls from the Atherosclerosis Risk in Communities Study (ARIC). The genetic ancestry of unrelated cases and controls was determined using RFmix. Participants from Project GENESIS or HCHS/SOL were identified as Latino if they had a European ancestry < 90%, an Amerindian ancestry < 90%, and if their African ancestry divided by their Amerindian ancestry was < 10 (Figure 1). All ES cases of Latino ancestry were included in analyses (49 of 406, 12%). Latino controls (2,229 of 2,596, 86%) were sampled at a 4:1 control:case ratio so that the distribution of Latino sub-populations matched that of the United States in 2010. This sampling procedure aimed to account for the diverse genetic ancestry of Latino sub-populations and the disproportionate selection of Latino groups into the HCHS/SOL cohort. The European set consisted of ES cases from Project GENESIS (n = 347) and controls from the ARIC study with a European ancestry > 90%. European controls were selected at a 4:1 control:case ratio (n = 1,388).

The association of 6 ES risk alleles was evaluated using additive genetic logistic regression models, with a p-value < 0.05 considered significant. The analysis of Latinos adjusted for European ancestry, African ancestry, and sex; Amerindian ancestry was not included because of multi-collinearity with European ancestry. The analysis of Europeans adjusted for these same covariates in addition to Amerindian ancestry. In Latinos, we then evaluated the effect of European or African ancestry proportions with ES risk, adjusting for sex and all 6 risk alleles. Finally, an admixture mapping analysis aimed to identify genomic regions with ancestral origins that differed in cases and controls.

Results: In Europeans, we replicated the effect of 5/6 risk alleles, with per-allele ORs for significant alleles > 1.65 (Table 1). In Latinos, we replicated the effect of 4 risk alleles with equally strong effect estimates (Table 1). Additionally, we observed a 15% decrease in the odds of ES for every 1% increase in African ancestry proportion (95% CI: 0.76, 0.93; Table 2). The admixture mapping analysis did not find genomic segments with differing ancestry at genome-wide significance but was under powered (Figure 2).

Conclusion: Our results support recent findings that several common variants contribute to ES risk and show their effects generalize to Latinos. We also report an inverse association between African genomic ancestry and ES risk in Latinos after controlling for known risk alleles, indicating that other ancestry-specific alleles may influence ES susceptibility and explain the observed racial disparities. Larger admixture mapping studies are needed to localize genomic regions that may harbor ancestry-specific risk alleles for ES.

Table 1. Multivariable OR and 95% CI for ES risk alleles in individuals of Latino or European ancestry.

			Latinos		Europeans		GWAS of ES*	
Region	GWAS SNP	Ref/Risk	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
1p36.22	rs113663169	C/T	3.7 (1.35, 12.5)	0.02	1.75 (1.35, 2.33)	< 0.01	2.05 (1.71, 2.45)	< 0.01
6p25.1	rs7742053	C/A	1.57 (0.8, 3.02)	0.18	1.65 (1.3, 2.09)	< 0.01	1.80 (1.48, 2.18)	< 0.01
10q21.3	rs10822056	C/T	1.76 (1.06, 2.95)	0.03	1.77 (1.48, 2.12)	< 0.01	1.76 (1.54, 2.02)	< 0.01
15q15.1	rs2412476	C/T	2.22 (1.32, 4)	<0.01	1.69 (1.39, 2.08)	< 0.01	1.73 (1.48, 2.01)	< 0.01
20p11.22	rs6047482	T/A	1.85 (1.09, 3.33)	0.03	1.72 (1.39, 2.17)	< 0.01	1.74 (1.49, 2.04)	< 0.01
20p11.23	rs6106336	T/G	1.78 (0.99, 3.21)	0.05	1.14 (0.88, 1.46)	0.32	1.74 (1.43, 2.12)	< 0.01

*Results from GWAS of ES (Machiela et al. 2018)

Table 2. Multivariable OR and 95% CI for a percentage point increase in European or African ancestry in Latinos

	OR (95% CI)
European	1 (0.98, 1.02)
African	0.85 (0.76, 0.93)

Logistic regression model included European and African ancestry proportions and adjusted for sex and 6 known risk alleles

Figure 1. Ancestry proportions of those identified as Latino.

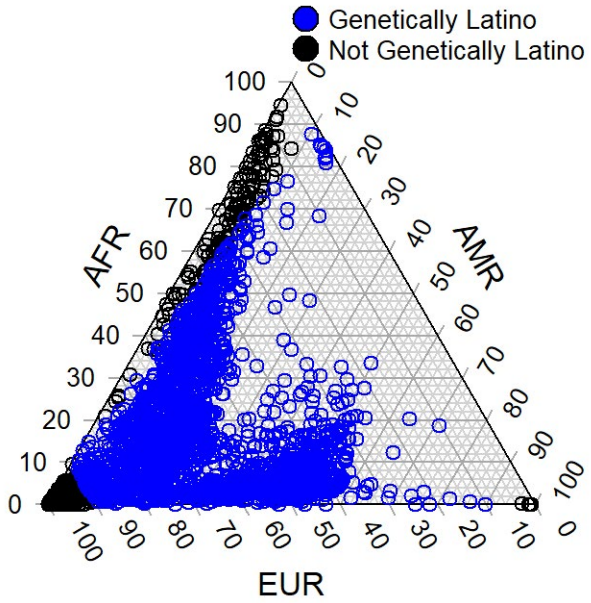
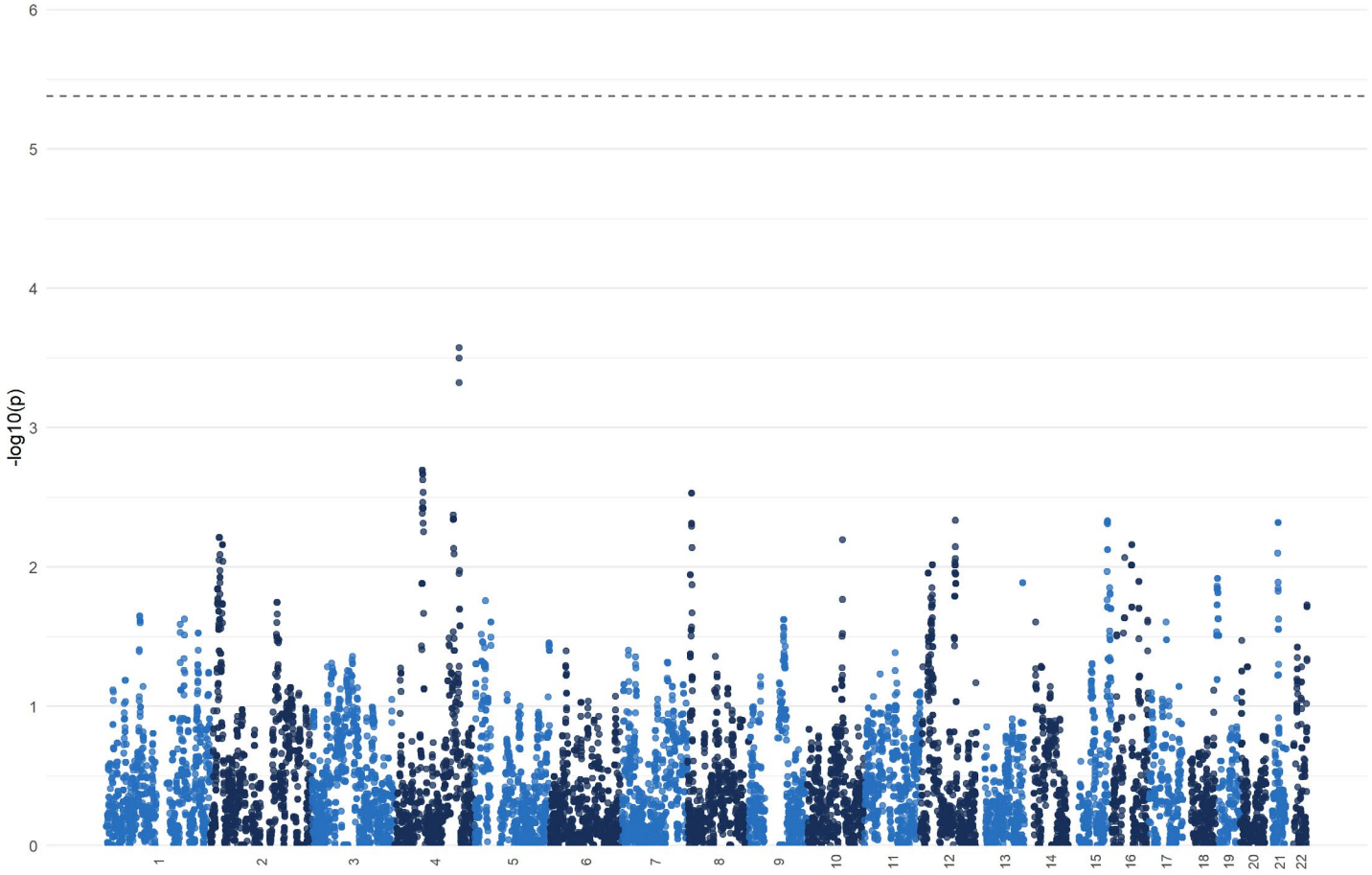


Figure 2. Results from admixture mapping analysis of local African ancestry in Latino cases compared to controls. Logistic regression is adjusted for global African ancestry proportion, global European ancestry proportion, and sex. Dashed line indicates statistical significance from Bonferroni adjustments.



Poster #195 3464895

DETERMINING THE CONTRIBUTIONS OF GENES CO-EXPRESSED WITH PD-L1 IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS) CASES IN THE TUMOUR-IMMUNE MICROENVIRONMENT

Victoria Coward[1], *Alice Ko*[2], *Maisha Syed*[5], *Nalan Gokgoz*[3], *Jay Wunder*[4], *Irene Andrulis*[1]
[1]*Molecular Genetics, University of Toronto, Toronto, Ontario, CANADA;* [2]*Laboratory Medicine and Pathology, University of Toronto, Toronto, Ontario, CANADA;* [3]*Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, CANADA;* [4]*Mount Sinai Hospital, Toronto, Ontario, CANADA;* [5]*Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, CANADA*

Objective: Sarcoma is arguably the most heterogeneous group of cancers with over 50 subtypes and as a result, survival rates have remained relatively stagnant in recent decades. Sarcoma treatment strategies rely on surgical resection, meaning immunotherapy interventions applied to other malignancies are largely underutilized. Some adult soft tissue sarcoma cases showed positive results in a clinical trial of the Programmed Cell Death 1 Receptor (PD-1) inhibitor, Pembrolizamuab, but some did not and it is unknown why certain patients did not respond at all[1]. A recent advance in the sarcoma field by Wunder *et al.* demonstrated that a subset of Undifferentiated Pleiomorphic Sarcoma (UPS) cases harboured tumour-infiltrating lymphocytes (TILs), expressed high levels of PD-1 ligand (PD-L1) RNA and had positive clinical outcomes[2]. Through RNA-sequencing, a list of differentially expressed genes between UPS cases with high and low PD-L1 expression was determined. Genes in the Th1 pathway were significantly active within this list. We hypothesize that tumour-related genes from the Th1 pathway may be related to an anti-tumour microenvironment. Our aims are to create and characterize patient-derived cell cultures to identify the potential roles of Th1 pathway genes in tumour-immune and tumour-stromal interactions by examining the functional differences in cytokine and chemokine output.

Methods: 300+ sarcoma specimens from untreated patients undergoing open biopsy or surgical resection have been collected for the isolation of both tumour cells and the respective TILs. Various dissociation and tumour culturing methods were optimized for each case, and methods were tested on multiple subtypes. After stable populations of UPS cells were grown, the cultured cells were validated using whole exome sequencing (WES) to confirm that they are malignant cells. The gene expression of PD-L1 and other Th1 pathway genes in bulk tumour and cultured cells were investigating using qPCR. An exploratory cytokine assay has been optimized to explore what chemical messengers may be differentially secreted between UPS cases expressing high and low levels of PD-L1. The functional differences in the tumour-secreted cytokines will be determined via autologous immune cell migration assays and angiogenesis assays using stromal cells.

Results: Due to the heterogeneity of sarcoma, optimal culturing conditions were variable. It was determined that culturing method and materials influence cell morphology (Figure 1), therefore techniques were optimized on a case-specific basis. This project utilizes viably-preserved tumour samples dissociated into small fragments. The fragments are plated in various culture conditions and the systems that yields a successful culture used going forward (Table 1). In accordance with Wunder et al. 2020, bulk tumours had Th1 pathway genes co-expressed with PD-L1 when assayed by qPCR (Table 2). Currently, differences in cytokine and chemokine production between different UPS cases are being assayed and analyzed.

Conclusion: A subset of resected patient samples are capable of forming successful cell cultures. Bulk UPS tumours co-express PD-L1 and Th1 pathway genes in both RNA-sequencing and qPCR experiments. Future experiments will determine if PD-L1 and co-expressed genes in UPS cells contribute to functionally different cytokine profile, that could in turn relate to distinct tumour-immune microenvironments.

Success By Subtype

Subtype	Successful	Total Cases Attempted
Undiff. Pleomorphic Sarcoma	9	11
Myxofibrosarcoma	8	12
Liposarcoma	2	3
Leiomyosarcoma	3	5
Misc.	3	5
Total	25	36

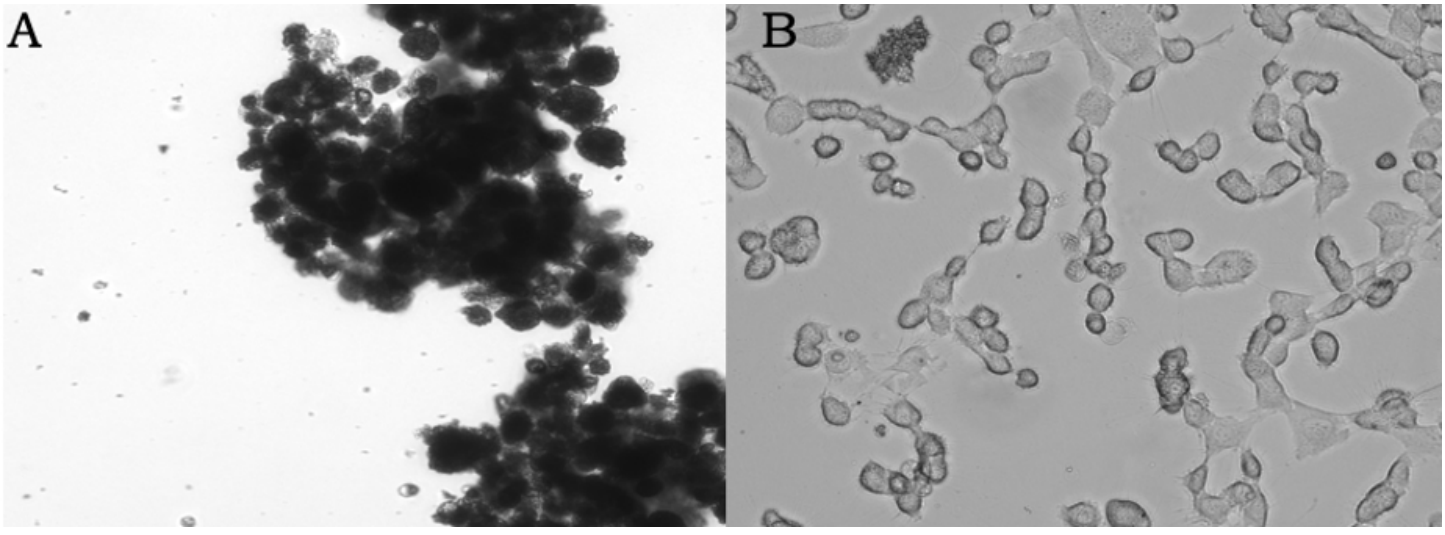
Table 1. A summary of sarcoma cases that have attempted to be cultured by subtype. A successful culture is defined as one that grows beyond 5 passages and produces more than 1x10^6 cells in that time.

UPS Gene Expression

Gene	PRKCQ		STAT1		PD-L1	
PD-L1 Status	Low	High	Low	High	Low	High
Mean gene expression	0.025	0.111	0.808	1.546	0.267	1.305
Observations	12	14	12	14	12	14
p value	0.044		0.017		0.003	

Table 2. 26 UPS cases were assayed for PD-L1 and 2 Th1 pathway genes – PRKCQ and STAT1, by qPCR. Th1 pathway genes were significantly differentially expressed when sorted by PD-L1 levels in the UPS subtype.

Figure 1. A Myxofibrosarcoma (MFS, sample 166) culture 72 hours after being plated in A) suspension or B) adherent media. Both cultures were preserved in liquid nitrogen and dissociated by tumour fragment method.



Poster #196 3464925

SARCOMA OF BONE ABOUT THE KNEE AND LIMB LENGTH IN PRE-ADOLESCENT PATIENTS: ALL OPTIONS STILL ON THE TABLE

Sean P. Kelly[2], *Dipak B. Ramkumar*[2], *Brooke Crawford*[3], *Santiago A. Lozano-Calderon*[1], *Megan E. Anderson*[2], *Mark C. Gebhardt*[2]

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Objective: In pediatric bone sarcomas the combination of increased survival due to chemotherapy and the effectiveness of limb salvage for local control has led to an increased focus on the prevention and management of limb length discrepancy (LLD). Reconstruction after sarcoma resection around the knee requires careful consideration given the significant contribution to axial growth of the distal femur and proximal tibia physes. Recent technological advances have focused on the increased use of expandable prostheses, however the ideal management of pre-adolescent bone sarcoma around the knee has yet to be determined.

Methods: A retrospective review was performed for all patients undergoing primary bone sarcoma resection about the knee (femoral to tibial diaphysis) from January 2000 to November 2015. Patients 12 years of age or younger at time of resection were followed until skeletal maturity. Exclusion criteria included age over 12, amputation as initial surgical treatment, and lack of follow-up through skeletal maturity. Diaphyseal lesions extending into the metaphysis were treated with intercalary allograft reconstruction, lesions including the epiphysis and less than a 5cm expected discrepancy underwent osteo-articular allograft, and patients with more than a 5cm discrepancy at skeletal maturity were treated with an expandable prosthesis.

Results: Twenty patients were followed to skeletal maturity and included 11 osteo-articular allografts, 5 expandable prosthesis, and 4 intercalary allografts. The average age at the index procedure was 10.3 years of age (range 6 to 12 years) with an average follow-up duration of 8 years (range 3.6 to 14.9 years) and a final mean LLD of 1.5cm (range 0 to 4.3cm). Four patients had an epiphysiodesis, two patients underwent femoral shortening, and 10 lengthenings were performed in the expandable prosthesis. 5 patients had a residual LLD over 3cm. There were a total of 7 revisions and 2 amputations.

Conclusion: Limb-salvage in pediatric bone sarcoma of the knee can be managed with multiple techniques producing satisfactory results in regards to limb-length inequality, with and without the use of a growing prosthesis. Careful pre-operative planning and shared decision making is a requisite given the high rate of secondary procedures for both limb-length and reconstructive failures.

Poster #197 3464936

REPEAT SURGICAL RESECTION FOR PATIENTS WITH RE-RECURRENT RETROPERITONEAL LIPOSARCOMA

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Objective: For recurrent retroperitoneal liposarcoma(RPLS), repeat surgical resection remains the mainstay of the treatment. However, the potential benefit of resection must be balanced against the associated morbidity and mortality of surgery. This study aimed to introduce the operative outcomes of patients with RPLS recurrences more than 2 times.

Methods: Medical records of re-recurrent RPLS patients who underwent at least 2 times of resectional surgeries previously were retrospectively retrieved from our database in our sarcoma referral center. Patients who did not undergo repeated surgical resections or presented with distant metastasis were excluded from our study. Data collected included demographics, histories of surgeries, operative outcomes, and pathological findings. Complications were evaluated via the Clavien-Dindo grade system. Risk factors related to postoperative fistula were analyzed through univariate and multivariate analysis.

Results: A total of 141 patients (male 71) were finally included in our study. The mean age was 55.1±0.9 years. All patients underwent an average of 2.9±0.1 times of sarcoma resectional surgeries previously. All patients received repeated surgical resections during this study after careful reviews of their histories and labs by a multidisciplinary sarcoma tumor board. The average maximum tumor dimension was 15.2±0.5cm with 75.9%(107/141) of multifocality. 141 patients received a total of 178 combined organ resections. The mean operative time was 386.4±11.7min and mean blood loss was 2845.4±276.1ml. 50.4%(71/141) patients developed various postoperative morbidities. Of these, 25/71 had severe complications with Clavien-Dindo grade≥3a. The most common complication was fistula (bowel fistula 12, urinal fistula 7, pancreatic fistula 3, gastric fistula 4, respectively). There were 2 patients deceased due to massive bleeding postoperatively. 76.6%(108/141) patients achieved R0/R1 resection. Pathological subtypes of liposarcoma were well differentiated (25), dedifferentiated (88), myxoid(9), pleomorphic(7), and mixed cell liposarcoma(12), respectively. Of which, myxoid liposarcoma was the only risk factor associated to postoperative fistula(p=0.006). There was no significant relationship between postoperative morbidity with age, gender, operative times, tumor size, and focality.

Conclusion: Repeat surgical resection for re-recurrent RPLS may be beneficial with relatively low incidence of morbidity and mortality. However, patients should be highly selected and operated by experienced sarcoma oncologists to seek optimal operative outcomes.

Risk factors related to postoperative fisular

Variable	N	Postoperative fistula	Postoperative fistula	P Value
		+	-	
Total	141	26	115	
Age(mean±SD)	55.1±0.9			0.767
Male Gender	71	15	56	0.407
Previous operative times				0.386
2	63	11	52	
3	42	12	30	
4	25	3	22	
≥5	11	0	11	
No. of Combined organ resections				0.800
0	34	7	27	
1	36	9	27	
2	36	5	31	
≥3	35	3	31	
Maximum tumor dimension(mean±SD)(cm)	15.2±0.5			0.722
Multi-focality	107	23	84	0.166
Blood loss(mean±SD) (ml)	2845.4±276.1			0.339
Operative time(mean±SD) (min)	386.4±11.7			0.757
R0/R1 resection	108	26	82	0.285
Pathological subtype Well Differentiated	25	2	23	
Dedifferented	88	14	74	
Myxoid	9	6	3	0.006
Pleomorphic	7	1	6	
Mixed	12	3	9	

Poster #199 3464982

ATRX PROMOTES AGGRESSIVE FEATURES OF OSTEOSARCOMA ACROSS SPECIES

Suzanne Bartholf DeWitt[1], *Sarah Hoskinson*[1], *Dharshan Sivaraj*[1], *Elaina J. Martz*[1], *Maya Sheth*[1], *Hailey E. Brighton*[1], *Robert W. Floyd*[2], *Brian E. Brigman*[1], *Ben Alman*[1], *Jason A. Somarelli*[2], *William C. Eward*[1]
[1]*Orthopaedic Surgery, Duke University, Durham, North Carolina, UNITED STATES;* [2]*Medicine, Duke University, Durham, North Carolina, UNITED STATES*

Objective: To understand how *ATRX* loss contributes to the aggressive features of osteosarcoma.

Methods: To better understand the mechanisms by which *ATRX* contributes to osteosarcoma aggressiveness, we used both *in vitro* and *in vivo* methods to examine changes in tumor initiation, growth and proliferation, migration, invasion and metastasis that correspond with loss of *ATRX* expression. An Osterix-Cre driven genetically engineered mouse model of OS was developed to examine tumor development in mice with loss of *Rb* and *p53* compared to loss of *Rb*, *p53*, and *ATRX*. Additionally, human 143B OS cells were stably transduced with non-silencing shRNA or one of two independent shRNA constructs for *ATRX* knockdown, and an *ATRX* knockout 143B cell line was generated using CRISPR-Cas9. Control and *ATRX* knockdown/knockout cells were injected subcutaneously in SCID-beige mice in Duke IACUC-approved studies, and tumor growth rates were compared. In an orthotopic model of osteosarcoma, SCID-beige mice were injected subperiosteally in the tibia with luciferase-labelled 143B wild-type or CRISPR knockout cells, and lung metastases were measured using IVIS imaging. In parallel, RNA-Seq was performed on the *ATRX* knockdown cell lines. CRISPR-Cas9 also was used to knock out *ATRX* in the human MG63 osteosarcoma cell line, and the wild-type or knockout MG63 cell lines were screened with 2,100 bioactive small molecule inhibitors to identify drugs for which *ATRX* loss of function led to increased drug efficacy. One drug of interest, an integrin inhibitor, was tested *in vivo* in an *ATRX*-null U2OS xenograft mouse model.

Results: In a genetically engineered mouse model, *ATRX* loss correlated with increased tumor initiation relative to wild-type *ATRX* expression. *ATRX* shRNA knockdown and CRISPR knockout in the 143B human OS cell line enhanced growth and local invasion of established xenograft tumors. The orthotopic mouse model showed increased lung metastasis in mice injected with the *ATRX* knockout cell line compared to wild-type. Whole transcriptomic profiling of the *ATRX* knockdown cell lines by RNA-Seq showed significant upregulation of the NF-κβ pathway, which has been shown to play a role in cancer cell proliferation, decreased apoptosis, and increased angiogenesis. Additionally, this sequencing showed significant downregulation of several extracellular matrix pathways, supporting a role for *ATRX* in matrix remodeling and invasion. Consistent with the RNA-Seq data, a drug screen of 2,100 bioactive small molecule inhibitors showed significant sensitization of the *ATRX* knockout to an integrin inhibitor. Interestingly, integrins are known key interactors with extracellular matrix components. An *in vivo* study with this integrin inhibitor showed reduced tumor growth compared to vehicle-treated mice.

Conclusion: Decreased *ATRX* expression in OS is associated with more aggressive tumors exhibiting increased proliferation, growth, migration, invasion and metastasis. Results from RNA-Seq and the bioactive drug screen support altered extracellular matrix remodeling, which may suggest a change in invasive properties of OS cells with *ATRX* expression loss. This is further supported by the integrin inhibitor study, showing increased sensitivity to this drug with *ATRX* loss. In the future, we plan to use both *in vitro* and *in vivo* methods to further explore the underlying mechanisms driving the aggressive phenotype observed with loss of *ATRX* expression.

Fig 1a: In an *Osterix-Cre* driven genetically engineered mouse model of OS, *ATRX* loss correlated with increased tumor initiation relative to wild-type *ATRX* expression. (Log-rank p=0.0021, ATRX floxed n=26 males and 25 females, ATRX wildtype n=22 males and 25 females).

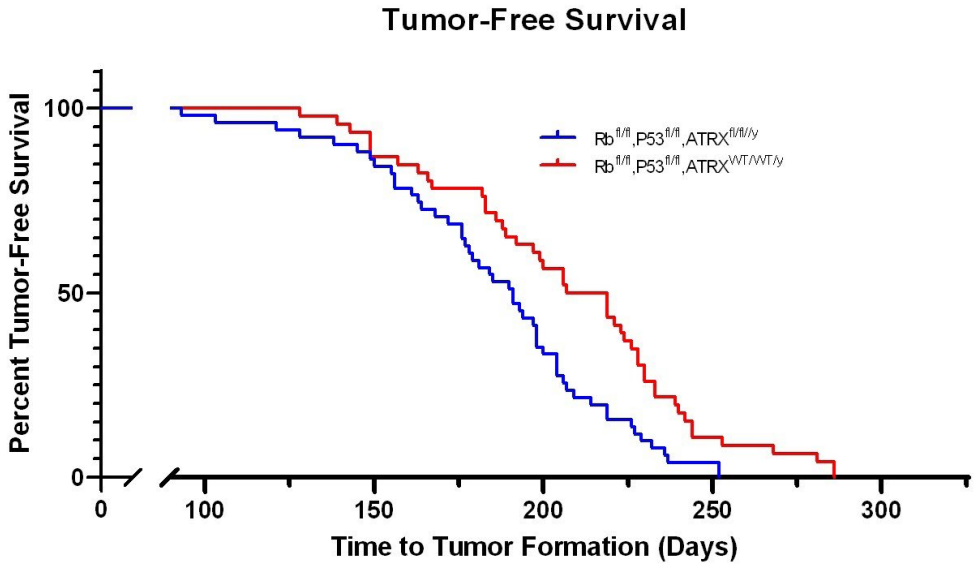
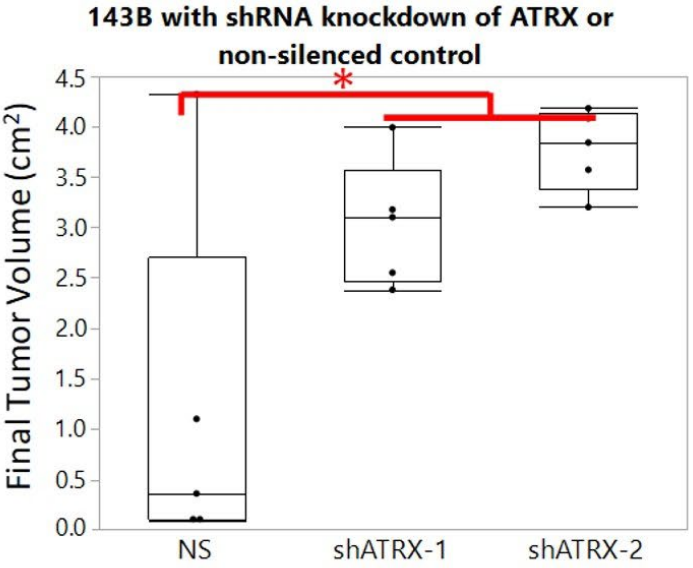


Fig 1b: *ATRX* shRNA knockdown and CRISPR knockout in the 143B human OS cell line enhanced growth and local invasion of established xenograft tumors.



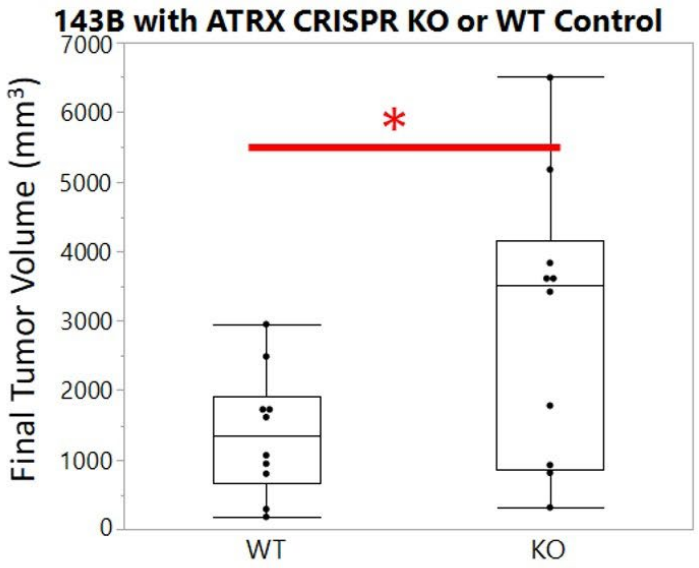
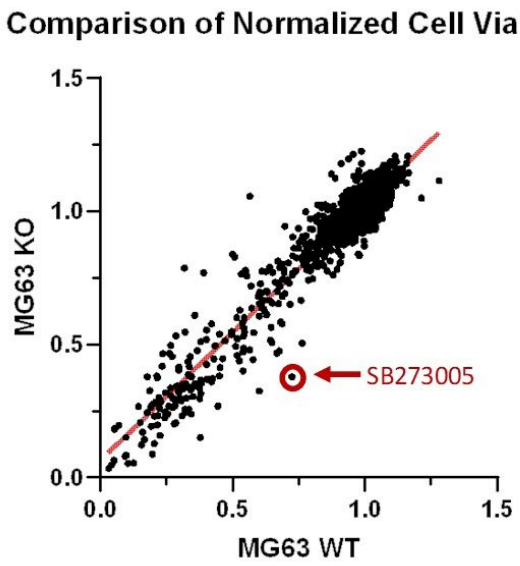
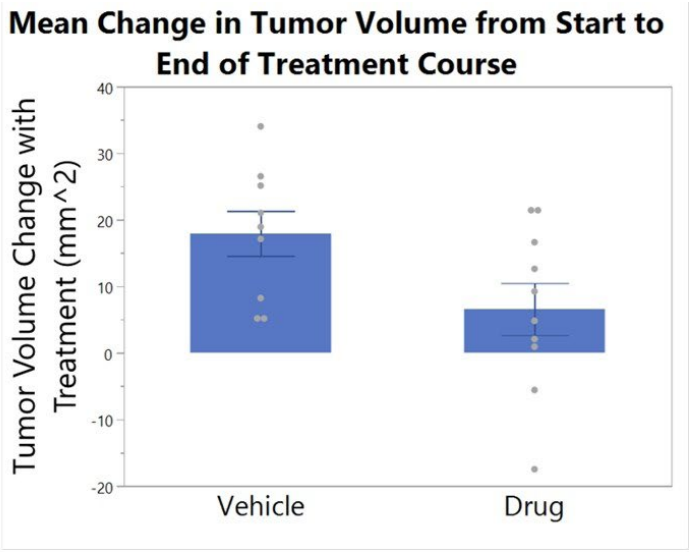


Fig. 2: Drug screen finds *ATRX* loss sensitizes OS cells to integrin inhibitor, SB273005, and our *in vivo* study shows decreased tumor growth with integrin inhibitor treatment.





Poster #200 3465022

TREATMENT STRATEGES IN PATIENTS WITH DESMOPLASTIC SMALL ROUND CELL TUMORS (DSRCT) IN THE FIRST LINE SETTING: A SYSTEMATIC REVIEW

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Objective: Desmoplastic Small Round Cell Tumor is a rare type of soft tissue sarcoma, which commonly affects males of young age. Treatment modalities vary substantially across published series, and they may include neoadjuvant chemotherapy, cytoreductive or debulking surgeries, intraperitoneal chemotherapy administration, high-dose chemotherapy infusions with autologous stem cell transplantation and whole abdominopelvic radiation. The objective of our systematic review was to analyze treatment modalities and efficacy outcomes of first-line therapies in patients with DSRCT.

Methods: Based on AMSTAR guidelines, a systematic literature search (PubMed/Ovid Medline) was performed with the following keywords "desmoplastic", "small", "round", "cell", and "tumor". Trial references were also screened to detect potential studies. Inclusion criteria were: prospective or retrospective studies that included patients with DSCRT in the first-line settings and that reported overall survival outcomes; Trials that provided general results, in which the overall survival of a certain treatment modality could not be determined, were excluded. Also trials that only included recent patients were not considered. When duplication of trials was suspected, considering demographic data of included patients, only the posterior study was included. Two authors independently reviewed the studies for inclusion. 3-year overall survival rates were calculated using Kaplan-Meier method. Random-effects meta-analysis was planned to estimate the 3-year overall survival in each treatment modality.

Results: Of 1139 studies screened, 20 eligible trials were found, including 323 patients with DSCRT diagnosis. The selected studies were published between 1991 and 2018, and 3 of them had a prospective design. In the selected studies, the first-line treatments that patients had undergone were chemotherapy (CT) +/- radiotherapy (RT) (n=46, 14%); cytoreductive/debulking surgery (S) and chemotherapy (n=43, 13%); S, CT and RT (n=19, 6%); S, CT and Hyperthermic intraperitoneal chemotherapy (HIPEC) (n=43, 13%); S, CT, HIPEC and RT (n=57, 18%); S, high dose chemotherapy with autologous stem cell transplant (CT/ASCT) (n=10, 3%); S, CT/ASCT and RT (n=33, 10%) and S, CT/ASCT, HIPEC and RT (n=21, 7%). Considering the manifest heterogeneity of the included population, and the different treatment schemes that were offered to the patients, we did not perform the quantitative synthesis.

Conclusion: Different treatment modalities are offered for patients with DSCRT in the first-line setting. The evident heterogeneity of the eligible studies, considering demographics of included population and different methods used to calculate outcomes, was a limitation of the present study. In our analysis, in institutions with larger number of participants, 3-year overall survival rates were numerically better than historical reports. Collaborative efforts and the creation of tumor registries is substantial to obtain further understanding of treatment efficacy in this rare disease.

Poster #201 3465049

THE PROGNOSTIC VALUE OF A NEW 4 GENE MOLECULAR PROFILE OF SEVERE HYPOXIA IN LOCALIZED HIGH GRADE SOFT TISSUE SARCOMA PATIENTS

Ninna Aggerholm-Pedersen[1], *Anna Jensen*[2], *Steffen Nielsen*[2], *Akmal Safwat*[1], *Brita Singer Sørensen*[2]
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[2]*Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus N, DENMARK*

Objective: Hypoxia has been identified as a prognostic factor of poor treatment outcome for patients with soft tissue sarcoma (STS), and may play a role in resistance to treatment including immunotherapy. Using molecular hypoxia profiles to establish clinically relevant hypoxia in sarcomas has only been explored to a limited extent. We have previously shown that a previously published 15 genes hypoxia profile developed in Head and Neck Cancer, has a clinical impact in sarcomas. The aim of this study was to test the oxygen dependency of the 15 genes included in the hypoxia signature, in order to determine genes, which can potentially serve as markers for severe hypoxia and test the value of this severe hypoxia profile in a clinical cohort of 110 localized high grade sarcoma patients.

Methods: The oxygen dependency of 15 genes profile was tested in vitro in four sarcoma cell lines, using a range of oxygen concentrations. For the analysis, the oxygen levels were divided into normoxia (5% O_2 and 21%O_2), moderate hypoxia (1%O_2 and 2%O_2) and severe hypoxia (0%O_2 and 0.5%O_2). Genes identifying severe hypoxia were chosen based on their relative expression level in severe relative to moderate hypoxia conditions in all cell levels. The prognostic value of these genes on disease specific survival (DSS) and overall survival (OS) were tested in a cohort of 110 patients with localized high-grad soft tissue sarcoma. The patients were allocated to 2 groups representing moderate and severe hypoxia.

Results: 4 genes (P4HA1, LOX, BNIP3 and EGLN3) showed increasing sensitivity to decreasing Oxygen concentrations allowing the stratification and distinction between moderate and severe hypoxia in all 4 cell lines.
The overexpression of these 4 genes was shown to be prognostic of poor overall and disease specific survival in the tested cohort of patients with localized high-grad soft tissue sarcoma. Compared to the previously published results of using the 15 gene profile in the same cohort we found the 4 gene profile to be equally prognostic to the 15 gene model.

Conclusion: The newly identified severe hypoxia 4 gene (P4HA1, LOX, EGLN3 and BNIP3) marker is predictive for poor prognosis in sarcoma patients.

Poster #202 3465050

THE DIAGNOSIS AND MANAGEMENT OF GASTROINTESTINAL STROMAL TUMORS IN INDIA: A SCOPING REVIEW

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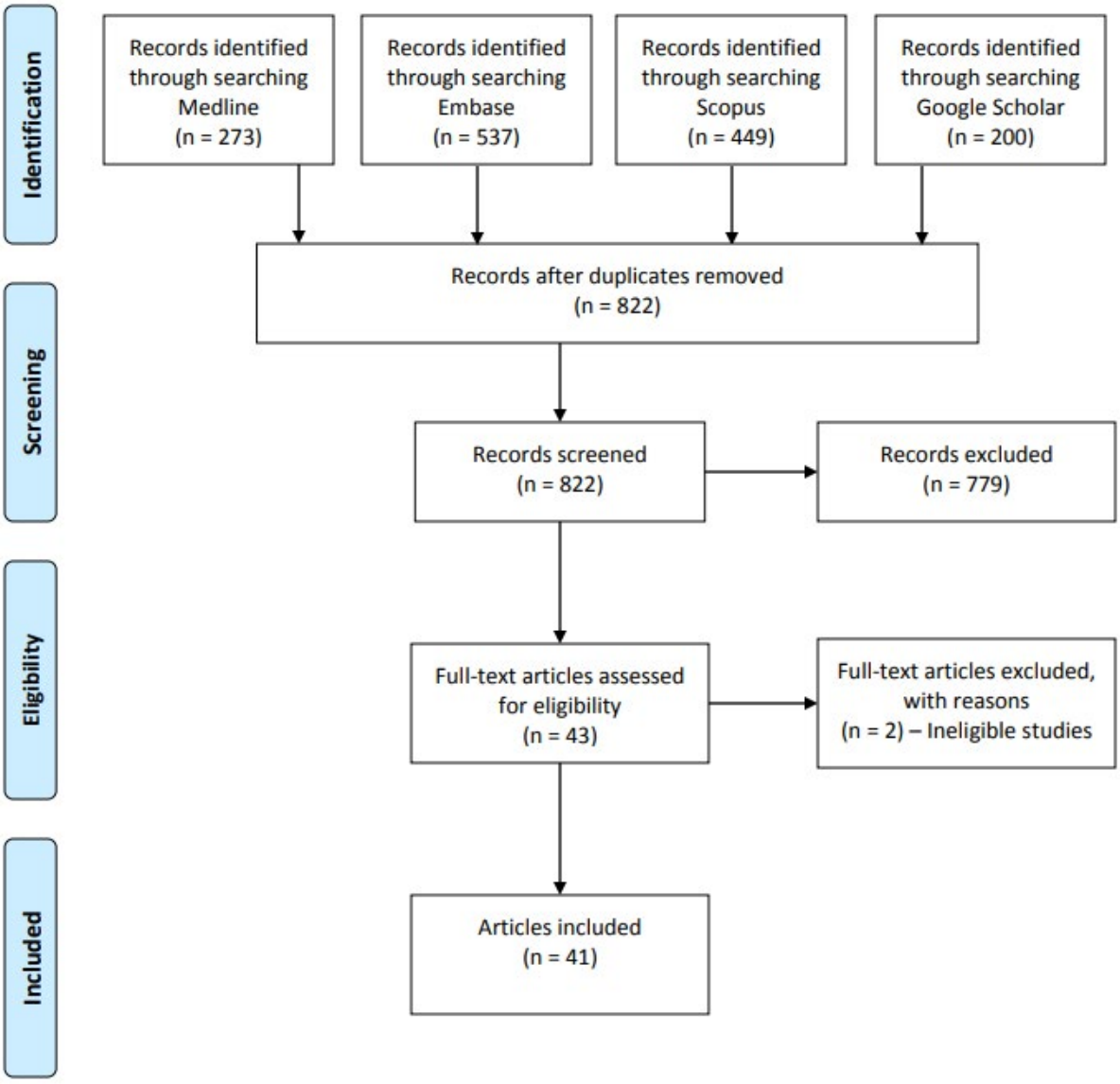
Objective: Gastrointestinal stromal tumors (GISTs) are the most common sarcomas of the gastrointestinal tract. This scoping review aimed to summarize all relevant studies from Indian centers focusing on the clinicopathological diagnosis and management of GISTs, to inform future research and improve patient management. We found this review necessary due to the scarcity of data regarding GISTs in India.

Methods: Scoping reviews are an excellent tool for mapping current knowledge and practices on a topic and identifying gaps in knowledge. This review has been conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews. All primary studies on the clinicopathological diagnosis and management of GISTs from India were included, irrespective of observational or experimental design, and prospective or retrospective nature, and limited to studies published in the English language from 2001 to 2020. Studies having less than 15 participants or focusing solely on radiological or surgical aspects related to GISTs were excluded. The electronic databases searched were Medline (PubMed), Embase, Scopus, and Google Scholar (up to the first 200 results). Two independent reviewers scrutinized search results.

Results: The search identified 41 studies from 22 Indian centers, consisting of 31 retrospective reviews and ten prospective studies. There were only two prospective clinical studies: one focused on the use of neoadjuvant Imatinib and the other on the safety and efficacy of Sunitinib in the second-line. There was no data on the prevalence of GISTs in India. Curiously, in six of the studies, the most common primary site was the small intestine, which does not agree with Western data. There was only one study on SDH immunohistochemistry among the articles screened, and this wasn't included in the review as it was only published as an abstract. There was no data on SDH-deficient GISTs. Ten studies included testing for KIT and PDGFRA exon mutations, and one study included cytogenetic analysis. Only two studies reported survival data for second-line therapy and one for third-line treatment. There were no multi-center studies or studies reporting the use of Regorafenib, Ripretinib, or Avapritinib. Few studies included the reporting of adverse events to Imatinib or subsequent lines of therapy. There were no randomized control trials dealing with GISTs.

Conclusion: While the developed world is making strides against GIST, with the approval of two new drugs just this year, we find it unconscionable that a country which accounts for over a sixth of the world's population is lagging far behind. Indian data regarding SDH-deficient GISTs and second/ third-line therapies is conspicuously absent. Nevertheless, rapid progress is still attainable with the help of dedicated clinics devoted to rare cancers, government support, collaborative efforts, and the involvement of patient support groups.

Figure 1. PRISMA Flow Diagram



Poster #203 3465057

THE DIAGNOSIS AND MANAGEMENT OF GASTROINTESTINAL STROMAL TUMORS IN INDIA: A PHASE 1/2 STUDY OF ABI-009 (NAB-SIROLIMUS) WITH PAZOPANIB IN PATIENTS WITH ADVANCED NONADIPOCYTIC SOFT TISSUE SARCOMAS

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Objective: ABI-009 (nab-sirolimus) consists of the Mammalian Target of Rapamycin (mTOR) inhibitor rapamycin encapsulated in an albumin nanoparticle. It recently demonstrated clinical activity in Perivascular Epithelioid Cell tumors (PEComas). Pazopanib (PAZO) is a multi-targeted, anti-angiogenic, tyrosine kinase inhibitor (aaTKI) that is approved in the United States for treatment of non-adipocytic soft tissue sarcomas (STS). Due to possible synergistic activity between mTOR and aaTKI, this clinical study was initiated to assess the feasibility and preliminary efficacy of co-administration of ABI-009 with PAZO in STS. Here, we report preliminary results of the phase I component of the study.

Methods: Eligible patients had a locally advanced or metastatic, non-adipocytic STS for which PAZO is indicated. Further, subjects must have (1) adequate end-organ function, (2) performance status 0-1, (3) one or more measurable target lesions (RECIST v1.1), (4) >1 and <5 prior systemic therapies for advanced disease, and (5) no prior treatment with mTOR or angiogenesis inhibitors. The phase I component of the trial follows a 3+3 design. Participants received PAZO 800 mg orally continuously on days 1-21 and ABI-009 intravenously on days 1 and 8. Initial ABI-009 dose cohorts, received 60, 45, and 30 mg/m^2 of ABI-009. Patients receive treatment on a 21-day cycle. Phase I primary endpoint is determination of a maximally tolerated dose of the combination. Secondary endpoints include adverse events characterization (CTCAE v5.0) and descriptive evaluation of objective responses and response duration.

Results: Six patients have been enrolled, with 2 in each dose cohort. Each developed dose-limiting toxicities (DLT), necessitating protocol-specified dose reductions. Four males and 2 female enrolled, with a median age of 56 years (range 47-73). Sarcoma histologies included myxofibrosarcoma (2), fibrosarcoma, solitary fibrous tumor, uterine leiomyosarcoma, and undifferentiated pleomorphic sarcoma.
DLT, all of which were grade 3, included thrombocytopenia (2), leukopenia/neutropenia (2), elevated lipase (1) and proteinuria (1). No grade 4 or 5 toxicities occurred. Grade 3 toxicities occurring in more than 1 episode included thrombocytopenia, neutropenia and proteinuria. Toxicities of any grade occurring in 5 or more episodes include: thrombocytopenia (20), neutropenia (9), proteinuria (9), diarrhea (9), oral mucositis (8), anemia (8), fatigue (7), hypophosphatemia (7), and acneiform rash (7).
All five patients discontinuing study therapy did so due to disease progression. Four patients discontinued therapy after2, 4, 4, and 6 cycles of study treatment. One of these four had progressive disease (PD) as best response, documented at first assessment after two cycles. The remaining three patients had stable disease (SD) as best response.
One patient (fibrosarcoma) demonstrated a partial response (PR) at first assessment after 6 weeks. This was sustained until 42 weeks/9 cycles of treatment, at which time PD was documented. Another subject (solitary fibrous tumor) had SD until 42 weeks after treatment initiation, at which time a PR was documented. This patient remains on treatment at the time of data cut-off after 54 weeks/18 cycles of treatment, receiving ABI-009 45mg/m^2/pazopanib 400 mg.

Conclusion: Thrombocytopenia, leukopenia/neutropenia, elevated lipase, and proteinuria have been identified as DLT in these three initial dose cohorts. Thrombocytopenia appears to be a prominent toxicity of the combination, and is known to occur with both agents. Despite these DLT, patients were able to receive continued therapy with this combination after protocol-specified dose modifications. This suggests that further dose exploration will successfully identify a recommended phase 2 dose for the ABI-009/PAZO combination. After protocol-specified dose modifications, four patients received at least 12 weeks of studyvtherapy, including two with objective PR. Updated information will be presented at the meeting.

Poster #204 3465078

SAINT: AN EXPANDED PHASE 2 STUDY USING SAFE AMOUNTS OF IPILIMUMAB (I), NIVOLUMAB (N), AND TRABECTEDIN (T) AS FIRST-LINE TREATMENT OF ADVANCED SOFT TISSUE SARCOMA [NCT03138161]

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Objective: Background: Sarcoma cells are most immunogenic earlier in the disease course and before treatment when the immune system can recognize and destroy them. The hypothesis is: Immune checkpoint inhibitors would be most effective when given as first-line therapy.

Objectives:
(1) To evaluate best objective response rate by RECIST v1.1 via CT scan or MRI,
(2) To assess progression-free survival (PFS) at 6 months; and
(3) To evaluate overall survival

Methods: Eligible patients for this Phase 2 study are males or females ≥ 18 years of age with locally advanced unresectable or metastatic soft tissue sarcoma, previously untreated, with measurable disease by RECIST v1.1. Immune checkpoint inhibitors I and N were given with T, a tumoricidal agent with defined doses of I (1 mg/kg i.v. q 12 weeks), N (3 mg/kg i.v. q 2 weeks), and T (1.2 mg/m2 i.v. q 3 weeks). The primary endpoints were: (1) Objective response rate by RECIST v1.1 via CT scan or MRI, (2) Progression-free survival (PFS): from first day of treatment to disease progression or death due to any cause; otherwise, it is censored at the time of last follow-up, and (3) Overall survival: from first day of treatment to death due to any cause; otherwise, it is censored at the time of last follow-up.

Results: Sixty-one subjects were included in this study. The median OS was >17.6 months and the median PFS was >6.7 months (6-month OS rate: 90%; 6-month PFS rate: 51%). Grade 3 TRAEs include fatigue (n = 6), adrenal insufficiency (n = 1), hyperglycemia (n = 1), dehydration (n = 1), hyponatremia (n = 2), bipedal edema (n = 2), increased AST (n = 6), increased ALT (n = 19), increased ALP (n = 1), port site infection (n = 2), psoriasis exacerbation (n = 1), anemia (n = 3), thrombocytopenia (n = 2), leukopenia (n = 1), and neutropenia (n = 3). Grade 4 TRAES include anemia (n = 1), neutropenia (n = 1), thrombocytopenia (n = 1), and increased CPK (n = 2). Grade 5 TRAES include rhabdomyolysis (n = 1). Therapy related AML occurred in one patient.

Efficacy Analysis of Evaluable Patients (n=60)
Best Response by RECIST v1.1
7 CR*, 8 PR, 37SD, 9 PD
*Two surgical CR

Best Overall Response Rate
24.6%

Disease Control Rate (%)
85.2%

Median Progression-free Survival, months (range)
>6.7 (1 – 25.8)

Median Overall Survival, months (range)
>17.0 (1 – 27)

Conclusion: Taken together, these data suggest that the three drugs are (1) synergistic, and (2) may be equal or superior to, and safer than, standard first line therapy for metastatic soft tissue sarcoma.

Poster #205 3465091

LANDSCAPE OF ALK FUSIONS IN SOFT-TISSUE SARCOMAS (STS)

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Objective: Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that can be constitutively activated via a fusion with a variety of gene partners. These fusions are implicated in oncogenesis of many cancers and targeted ALK therapy is available. Beyond inflammatory myofibroblastic tumors (IMT), the incidence and distribution of ALK fusions in sarcomas is poorly understood. Here we undertake the largest evaluation of ALK fusions to date in STS.

Methods: The Oncology Research Information Exchange Network (ORIEN) is a collaboration of 19 member institutions formed to share real world data (RWD) and clinical outcomes for patients with advanced cancer. The ORIEN AVATAR program, launched in 2016, generates comprehensive whole-exome sequencing (WES) and transcriptome sequencing (RNA-Seq) for a subset of high-risk patients, including >1000 patients with STS, enrolled at ORIEN member institutions. We evaluated the landscape of ALK fusions identified using the RNA-Seq genomic pipeline for STS patients in the ORIEN Avatar program. A consensus calling methodology (STARfusion, Arriba) was implemented for fusion detection. Only high-quality putative fusions were included in the analysis. High-quality is measured using (Fusion Fragments Per Million total reads) FFPM ≥0.1 and a high or medium confidence score from Arriba indicating that the fusion prediction has an associated likelihood that the transcript is aberrant (not previously identified in healthy tissue), has underlying evidence for genomic rearrangement, and is not an artifact.

Results: Of 1037 soft-tissue sarcoma patients profiled, representing 76 distinct STS histologies, 12 ALK fusions were noted which translates to an overall incidence of 1.2%. Histologies included myxoid liposarcoma (MLS) (7/48), leiomyosarcoma (2/143), IMT (1/25), well-differentiated liposarcoma (1/36), undifferentiated sarcoma (1/64). Male:Female ratio was 7:5. Median age at diagnosis was 53.6 years (34.3 to 66.4). ALK was fused to 7 different partner genes with lnc-ALK-1 being the most common. Other binding partners are noted in the table. 7/11 pts were metastatic at presentation. 9/11 patients with ALK fusion remain alive after median 3.1 years follow-up. Each of 2 deceased patients had OS 2.9 and 3.3 years. One LMS pts had ALK fusion confirmed by clinical grade testing and treated with Crizotinib. Of note, lnc-ALK-1 was present in all 7/48 (14.5%) MLS. All contained the pathognomonic FUS-DDIT3 fusion.

Conclusion: Consistent with prior reports, ALK fusions are a rare event in sarcomas seen in the previously reported LMS and IMFT subtypes. Interestingly, the lnc-ALK-1 gene was also seen commonly in myxoid liposarcoma. Further work to characterize the mechanism of this fusion is warranted.

ALK FUSIONS PARTNERS IN STS

ALK fusion partners	Count	Description	Biotype	STS Subtype
lnc-ALK-1 (AC016907.2)	7	Novel target	lncRNA	Myxoid liposarcoma
USP34	1	Ubiquitin Specific Peptidase 34	Protein Coding	Undifferentiated Sarcoma
IGFBP5	1	Insulin Like Growth Factor Binding Protein 5	Protein Coding	Spindle cell sarcoma (IMFT)
AC005165.1	1	Novel Transcript	lncRNA	Leiomyosarcoma
HEATR5B	1	HEAT Repeat Containing 5B	Protein Coding	Leiomyosarcoma
SLC37A3	1	Sugar phosphate exchanger 3	Protein Coding	Leiomyosarcoma
FOSL2	1	Fos-related antigen 2	Protein Coding	Leiomyosarcoma

Poster #206 3465105

ANGIOSARCOMA TREATMENT USING PROPRANOLOL: A SINGLE INSTITUTION EXPERIENCE IN ARGENTINA

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Objective: Angiosarcomas (AS) are uncommon soft tissue tumors of endothelial cell origin. Standard systemic treatment is chemotherapy based on paclitaxel or doxorubicin with a median progression-free survival (PFS) of 3.7-5.4 months. The overall response rate to first-line was around 30%, and less than 10% in subsequent lines. Effectivity of synergistic treatment with the β-blocker propranolol and chemotherapy was previously studied, including paclitaxel, vinblastine, vinorelbine, methotrexate, doxorubicin, or gemcitabine. The objective of this study was to describe a cohort of patients with AS treated with propranolol plus chemotherapy, evaluating the clinical characteristics and outcomes.

Methods: Patients with pathologically confirmed advanced AS treated with chemotherapy plus propranolol were selected retrospectively from the Alexander Fleming Cancer Institute (Buenos Aires, Argentina), between 2000 and 2017. Clinical characteristics and outcomes were recovered from medical records. The Kaplan–Meier method was used to estimate the median PFS of propranolol plus chemotherapy, defined as the time from treatment initiation to the first documented disease progression.

Results: Among 13 patients included, the median age was 62 years (IQR 59-77), and the majority were females (n=11, 85%). All patients have a confirmed AS diagnosis by immunohistochemistry (CD34/CD31). No molecular tests were performed. Most of tumors were well-differentiated (n=11, 85%), and only two patients (15%) had a poorly differentiated AS. Distribution of locations was: AS of the breast (radiation-induced) (n=5, 38%), extremities (n=4, 31%), intra-abdominal (n=2, 15%), thoracic wall (n=1, 8%), and head and neck (n=1, 8%). Three patients (23%) were diagnosed at advanced stages and ten (77%) with loco-regional disease.
Six cases (47%) were selected for treatment efficacy analyses using propranolol plus vinorelbine (n=2, 33%), vinblastine + methotrexate (n=2, 33%), vinblastine (n=1, 17%), or thalidomide (n=1, 17%). Local treatments, such as surgery, radiotherapy, or isolated hyperthermic limb perfusion were used pre or post propranolol and chemotherapy in five (83%) and two (33%) patients, respectively.
Combined propranolol and chemotherapy were used as first-line treatment in two cases (33%), and as second or third-line in three (50%) and one (17%) patients, respectively. Median treatment lines for these patients was 4 (IQR 2-6). A heavily pretreated patient, progressed to five lines of therapy, was exposed to atezolizumab, achieving a complete response. Interestingly, this tumor had a high tumor mutation burden (59 mt/mb). Grade I-II chemotherapy-induced adverse events were observed in the entire population, including asthenia and leukopenia. No grade III-IV adverse events were developed.
Disease control rate was 67% (complete response 33% [2/6], partial response 33% [2/6], and progression disease 33% [2/6]). The median PFS to propranolol plus chemotherapy was 2.43 months (95% CI 1.55-3.31).

Conclusion: In our experience, the combination of propranolol and chemotherapy was a suitable strategy for the treatment of advanced AS, with a considerable response rate and an expected toxicity profile. This strategy needs to be evaluated in randomized clinical trials.

Poster #207 3465109

SQ3370, A NOVEL APPROACH TO LOCALLY CAPTURE AND ACTIVATE CYTOTOXIC DRUGS, PRODUCES SUSTAINED RESPONSES IN INJECTED AND NON-INJECTED LESIONS VIA IMMUNE ACTIVATION IN PRECLINICAL MODELS

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Objective: Conventional chemotherapy is the gold standard for treating a variety of solid tumors, but it's effectiveness is limited by systemic off-target toxicity. Here, we present **SQ3370**, a **modular chemistry-based approach** that allows the capture and activation of therapeutics at a tumor site. In contrast to mAbs, ADCs, and other targeted/precision medicine approaches, SQ3370 is independent of biomarkers, enzymatic activity, pH or oxygen levels. SQ3370 consists of a local intratumoral injection of a prodrug-capturing biomaterial (SQL70) followed by 5 daily systemic infusions of SQP33, an attenuated prodrug of doxorubicin (Dox). Complementary chemical groups in the 2 components allow the local capture of the prodrug and trigger release of active Dox at the tumor site. Through this local activation approach, SQ3370 allows higher doses to be given systemically with reduced side effects, overcoming the toxicity limitations of conventional Dox. Our team first introduced the concept1 and showed enhanced safety and efficacy in a mouse fibrosarcoma model2. Here, we show that **SQ3370 produces a sustained anti-tumor response against both injected and noninjected lesions.** In addition, we show the pharmacokinetic (PK) profile and tolerability of SQ3370 given at high doses in different species.

SQ3370 is being tested in a Phase I open-label dose escalation first-in-human clinical trial in patients with advanced solid tumors. (A separate trial-in-progress abstract has been submitted.)

References: 1. JM Mejia Oneto, et al., Acta Biomaterialia, 2014. 2. JM Mejia Oneto, et al., ACS Central Science, 2016.

Methods: The pharmacokinetic profile of SQ3370 was evaluated in rats and the safety profile of SQ3370 was evaluated in dogs, the most relevant species for Dox. In mice, two subcutaneous flanks were inoculated with MC38 tumor cells. One tumor was injected with SQL70 biomaterial, while the other remained non-injected. SQP33 was then given in 5 daily intravenous doses. Tumors were harvested from a subset of mice at 2 weeks and were assessed for infiltrating immune biomarkers.

Results: The greater safety of SQ3370 allows significantly higher doses to be administered compared to conventional Dox. The PK profiles in rats demonstrated that SQL70 biomaterial efficiently captures and activates the prodrug. Safety evaluation in dogs showed that **SQ3370 allowed up to 8.95-fold increase in Dox dosing** with minimal systemic adverse events including cardiotoxicity. Further, in mice bearing two flank tumors, SQ3370 significantly **increased** median **overall survival** and s**ustained tumor regression of injected and non-injected tumors.** Tumor biomarker analyses indicate immune activation with i**ncreased total infiltrating T cells** in both lesions, increased CD8+ T cells in the injected lesions and decreased regulatory T cells in the non-injected lesions. Together, the data suggest that the anti-tumor response is mediated by immune activation via i**mmunogenic cell death** (ICD).

Conclusion: SQ3370 is a novel therapeutic modality to treat solid tumors by using a known effective cytotoxic, Dox, and unlocking its dosing capabilities while minimizing its off-target toxicity. **SQ3370's systemic anti-tumor effect** could greatly benefit patients with undetectable micro-metastatic or widely disseminated lesions. SQ3370 is the first proof-of-concept of the local capture and activation technology. In the future, **this platform** could be applied to **a variety of cytotoxics** and other anti-cancer drugs i**mproving their efficacy and minimizing their systemic toxicity**.

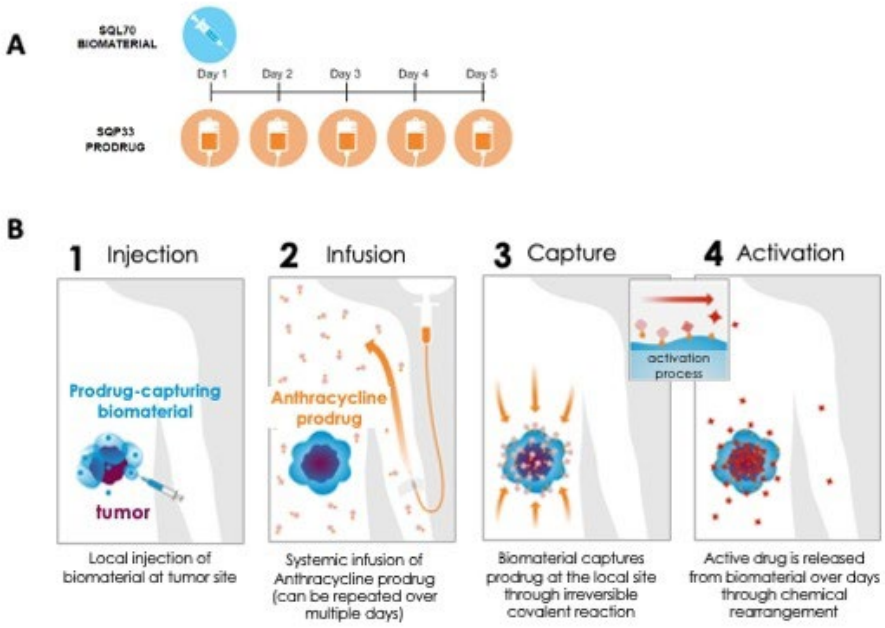
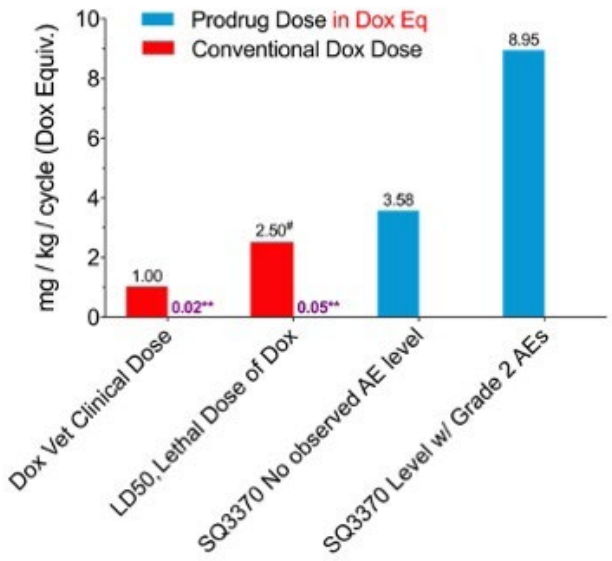


Figure 1. SQ3370 Investigational Product. (A) Treatment cycle and (B) Mechanism of Local Capture and Activation.

Abstract ID - 3465109



* Doxorubicin exposure to tumor,
* C. Bertazzoli et. al. Toxicol. Appl. Pharmacol, 1985; 79:412-422.
** C. Li et. al. J. Nuc. Med. 1997, 38, 1042 - 1047
ζ Grade 2 AE level corresponds to highest non-severely toxic dose (HNSTD)
Dox Eq = Doxorubicin equivalents

Figure 2. Dose Comparison of SQ3370 with Conventional Doxorubicin in Dogs (GLP Toxicology)

Abstract ID - 3465109

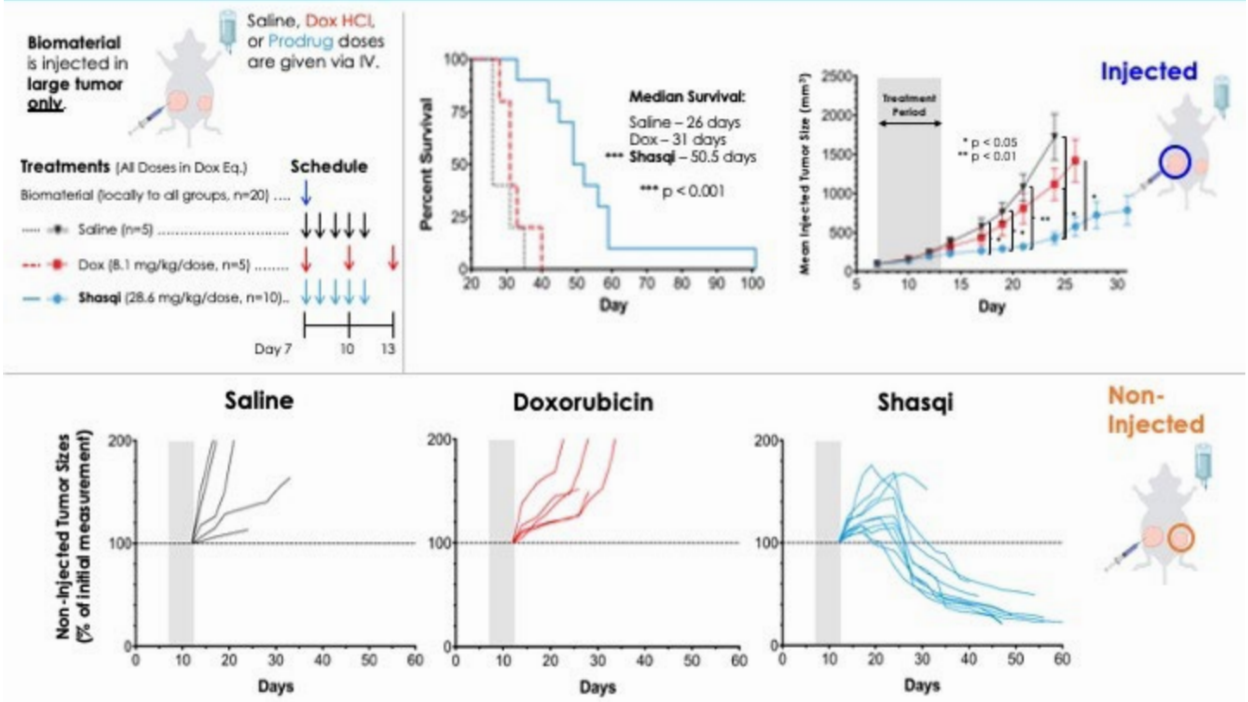


Figure 3. SQ3370 induced systemic anti-tumor response Injected and Non-Injected syngeneic mouse tumors

Poster #208 3465112

EWS/FLI DRIVES DYNAMIC REORGANIZATION OF LSD1 AND REST IN EWING SARCOMA CELLS

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Objective: Pediatric sarcomas frequently harbor quiet mutational landscapes and are characterized instead by sole driver events such as the mutation of critical chromatin regulators, expression of oncohistones, or chromosomal translocations resulting in the expression of oncogenic fusion proteins. Ultimately, these events promote malignancy through disruption of normal gene regulation and development. The driver protein in Ewing sarcoma, EWS/FLI, is an oncogenic fusion and transcription factor that reshapes the enhancer landscape, resulting in widespread transcriptional dysregulation. REST is a chromatin repressor complex that repressed neuronal genes in non-neuronal tissues and is highly expressed in Ewing sarcoma. REST functions independently of EWS/FLI to promote vascular function and promoting tumor growth and metastasis. LSD1 is both a component of the REST corepressor complex and a critical functional partner of EWS/FLI, and inhibition of LSD1 results in impaired EWS/FLI function and Ewing sarcoma cell death. Preliminary data suggested that EWS/FLI expression disrupted the normal association of LSD1 and REST. We wanted to reproduce this data with an orthogonal technique and assess the interaction of LSD1 and REST using our knockdown-rescue system.

Methods: We used shRNA-mediated depletion of EWS/FLI in A673 cells coupled with either a mock rescue or ectopic expression of wildtype EWS/FLI to generate cells. We then assayed these cells using cleavage under targets and tagmentation (CUT&Tag) to determine the genomic localization of REST and LSD1 in cells with wildtype, depleted, or rescued levels of EWS/FLI expression. We further used these cells to perform co-immunoprecipitations to evaluate the stability of the LSD1-REST interaction.

Results: Contrary to our preliminary data gathered with ChIP-seq, we found that LSD1 and REST commonly colocalize in both the presence and absence of EWS/FLI. Co-IP experiments show that the LSD1 and REST complex is stable with varying levels of EWS/FLI. Instead, EWS/FLI expression causes a dynamic, genome-wide reorganization of LSD1 and REST.

Conclusion: Our findings suggests that previous attempts to capture genome-wide localization of chromatin regulators using ChIP-seq need to be interpreted with caution, as they may be contain significant artifact as a result of fixation and sonication. By using a technique which does not require these steps, we were able to collect data with a higher signal-to-noise ratio and show dynamic reorganization of different chromatin regulators, LSD1 and REST. These data suggest that LSD1 is important for the functioning of both EWS/FLI and REST in Ewing sarcoma cells, and inhibition of LSD1 may alter both of these pathways simultaneously.

Poster #209 3465136

HEAD AND NECK ALVEOLAR RHABDOMYOSARCOMA – A RARE ENTITY

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Objective: Rhabdomyosarcoma (RMS) is a rare tumor, accounting for 2 to 5% of all soft tissue sarcomas (STS) in adults. About 40% of RMS appear in adults, being more frequent in head and neck. Treatment usually involves surgery, radiation and chemotherapy. We describe the experience of a tertiary university hospital in the diagnosis and treatment of alveolar RMS of the head and neck.

Methods: Retrospective analysis of the cases of alveolar RMS of the head and neck treated in our Oncology Department, between January 2015 and December 2019.

Results: Two cases of locally advanced head and neck alveolar RMS were identified:
Case 1: A 59-year-old woman with an expansive lesion centered on the right nasal cavity (4 cm longest diameter), with orbital wall invasion, causing proptosis, whose biopsy revealed an alveolar RMS. Staging: stage I, group III, intermediate risk of recurrence. She was treated with 5 cycles of induction chemotherapy with VAI (vincristine, dactinomycin and ifosfamide), with visible clinical response, proptosis resolution and acceptable toxicity. She underwent surgical wide-margin resection and lymphadenectomy. Pathology showed a complete pathological response, and adjuvant radiotherapy was omitted. She completed 2 cycles of postoperative chemotherapy with VAI and at the date of this analysis has no evidence of recurrence.
Case 2: A 19-year-old man with a progressively growing ulcerated craniofacial mass, severe local pain, dysphagia and cachexia in 5 months. Craniofacial MRI showed a tumor on the right maxillofacial region (12 cm longest diameter), with orbital wall and intracranial invasion (dural and parenchymal). Biopsy was compatible with alveolar RMS. Staging: stage I, group III, intermediate risk of recurrence. He was started on palliative chemotherapy with CAV (cyclophosphamide, doxorubicin and vincristine). At the date of the analysis he performed two cycles, with partial response and clinical improvement.

Conclusion: The described cases of head and neck alveolar RMS were locally aggressive but with a high rate of response to chemotherapy. Surgery is usually very mutilating and can lead to functional morbidity. Neoadjuvant chemotherapy is important to facilitate surgery and to allow a curative intent.

Poster #210 3465158

PROMIS-10 SURVEY T-SCORES AND UNPLANNED HOSPITAL ADMISSION/EMERGENCY ROOM VISITS

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Objective: Our research study is focused on determining the relationship between PROMIS-10 scores for patients with sarcoma and unplanned admissions/ER visits and mortality data.

Methods: Within a sarcoma medical oncology clinic, we collected the raw and T-scores of these PROMIS-10 surveys for this pilot study. We also collected unplanned hospital admission/ER visit and mortality data for each patient, without patient identifiers. We performed a descriptive analysis of the data and are evaluating the PROMIS-10 survey T-scores and the next unplanned hospital admission and/or ER visit (within one week, two weeks or 30 days) and date of death.

Results: For all patients with an unplanned hospital admission/ER visit, the median Global Physical T-score was 42.3 (range: 16.2 – 67.7). The median Global Mental T-score was 45.8 (range: 21.2 – 67.6). The median Global Physical T-score prior to date of death was 34.9 (range: 23.5 – 50.8). The median Global Mental T-score prior to date of death was 43.5 (range: 33.8 – 67.6).

Conclusion: We showed that we are able to obtain worthwhile data to objectively evaluate patient's physical and mental well-being through survey data during cancer treatment. We are currently performing further exploratory analyses on specific scores that can serve as predictive markers for treatment-related complications.

Poster #211 3465174

SORAFENIB IN DESMOID TUMOR: A BRAZILIAN CANCER CENTER EXPERIENCE

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Objective: We aimed to evaluate the safety profile and efficacy of sorafenib in patients with diagnosis of desmoid tumor treated in a Brazilian cancer center.

Methods: We performed a retrospective analysis of patients with histologically confirmed desmoid tumor treated with sorafenib in our center between January 2008 and May 2020. Clinical variables were age, gender, tumor location, history of familial adenomatous polyposis (FAP) disease, previous treatments. Efficacy was evaluated by tumor shrinkage according to RECIST criteria. Time-to-treatment discontinuation (TTD) was considered the interval from initiation of sorafenib to discontinuation due to tumor progression, adverse events, physician and/or patient choice, or patient death. Toxicity was evaluated according to CTCAE v3.0.

Results: Twenty patients with desmoid tumor treated with sorafenib were included. Median age at diagnosis was 35.5 years (range: 13 – 69 yo); 13 were female (65%) and 7 male (35%). Three patients had a diagnosis of FAP. Sites of primary lesion were: lower extremity (n=5; 25%), abdominal wall (n=5; 25%), intra-abdominal (n=4; 20%), thoracic wall (n=3; 15%), upper extremity (n=2; 10%), abdominal wall and intra-abdominal (n=1; 5%). Sorafenib was used as first-line systemic therapy in seven patients (35%), second-line in nine (45%), and in third-line in four patients (20%). Five patients received previous chemotherapy (25%), five patients received previous radiotherapy (25%), and eleven patients (55%) underwent surgery as first treatment. The median follow up period for the entire cohort was 59.2 months (IQR: 87.7 – 25). Considering RECIST criteria, three patients had partial response (15%), fourteen patients had stable disease (70%) and one patient had progressive disease (5%). Two patients discontinued sorafenib before first response assessment due to toxicity. No complete response was seen. Six patients presented sustained clinical response after sorafenib discontinuation; median time of sorafenib use in these six patients was 38.1 months (IQR: 53 – 25) and the median follow up period after sorafenib discontinuation and with no treatment was 7.7 months (IQR: 19.4 – 3.1). No statistically significant correlation could be stablished between clinical variables and response by RECIST. Median TTD was 12.3 months (IQR: 38.1 – 1.8). Nineteen patients (95%) presented any adverse event during sorafenib treatment. Four patients (20%) discontinued treatment due to grade 3 toxicities, which were fatigue, maculo-papular rash, hand-foot syndrome and diarrhea. Most common grade 1 and 2 toxicities were: diarrhea (55%), hand-foot syndrome (30%), rash (30%), alopecia (25%), fatigue (20%) and nausea (15%). Three patients had toxicity managed with dose reduction of sorafenib and maintained treatment benefit. No grade 4 toxicities were reported. Seven patients were still in treatment with sorafenib at the end of follow up period.

Conclusion: Our data from a single institution analysis of patients outside clinical trials treated with sorafenib showed a safe profile of toxicity. In our cohort, one third of patients used sorafenib in first line. Stable disease was the best response in the majority of patients. The best treatment duration is not well defined and our data showed that the median duration was 12 months, with 30% of patients presenting a sustained clinical response after sorafenib discontinuation. Further studies are needed to define the best treatment sequence and duration of treatment.

Poster #212 3465223

SILVER-COATED MEGAPROTHESES IN THE MITIGATION OF PROSTHETIC JOINT INFECTIONS – A COST-EFFECTIVENESS ANALYSIS

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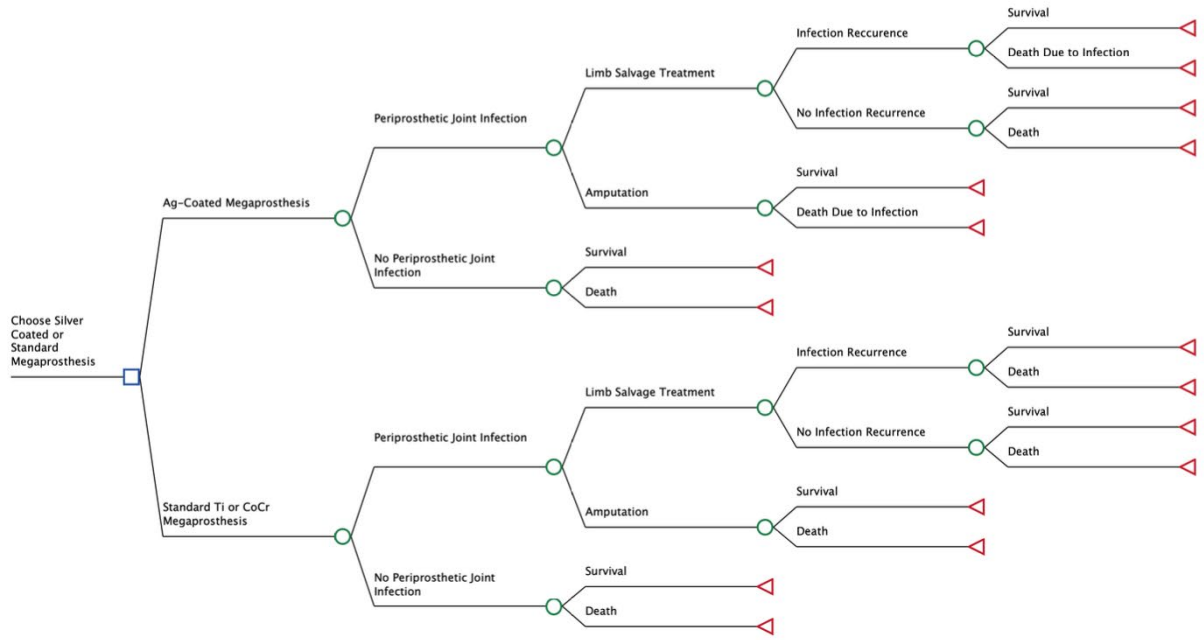
Objective: Limb salvage surgery with endoprosthetic reconstruction remains an effective local treatment option for lower extremity bone sarcomas. Prosthetic joint infection (PJI) remains a common mode of failure for these reconstructions. Elemental silver has native antimicrobial properties and the addition of silver coating to implants has demonstrated some advantages in decreasing the incidence of PJI but comes at significant cost. We aimed to demonstrate the cost-effectiveness of silver-coated megaprostheses in mitigating PJI.

Methods: An expected value cost-effectiveness analysis was performed with payoffs of 1) direct medical costs in 2020 USD and 2) total effectiveness in quality-adjusted life expectancy (QALE).The cost-effectiveness analysis was conducted using decision analysis software (Figure 1). A willingness to pay (WTP) threshold of USD $100,000 was utilized for all analyses, based on currently accepted practice. Probability, quality, and cost paramters were abstracted from a comprehenisve, systematic literature review. Tornado analysis was performed to ascertain the variables with greatest influence and additional one-way and two-way sensitivity analysis was performed to ascertain the effect of their variation.

Results: The total cost was $45,446.83 and $64,254.45 USD and total QALE was 12,085.53 and 12,169.66 days for the standard and silver-coated prostheses, respectively. Based on this analysis, the use of silver-coated megaprostheses confers an incremental cost-effectiveness ratio of $114.12 USD per quality adjusted life day (QALD).

Conclusion: Considering our willingness to pay threshold of $100,000 USD, the use of silver coated megaprosthesis is cost-effective at minimizing the incidence and associated complications of prosthetic joint infections in this population.

Figure 1. Decision Tree Model Comparing Silver-Coated Megaprosthesis Versus Standard Megaprosthesis.



Poster #213 3465226

LEVERAGING EVOLUTIONARY FITNESS BOTTLENECKS AS THERAPEUTIC VULNERABILITIES IN DOXORUBICIN-RESISTANT OSTEOSARCOMA

Etienne M. Flamant[1], *Anika Agarwal*[2], *Anna Slingerland*[2], *Ella Gunnady*[2], *Abbey Milwicz*[2], *Cameron Bozdog*[2], *Maya Sheth*[2], *Kathryn E. Ware*[2], *Mark M. Cullen*[1], *David Corcoran*[3], *Joseph Prinz*[3], *Nicolas Devos*[3], *William C. Eward*[4], *So Young Kim*[5], *Jason A. Somarelli*[2]

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Objective: Osteosarcoma is a highly aggressive, heterogeneous primary bone malignancy that is most common in children and adolescents. The past 40 years have seen little improvement in the prognosis of osteosarcoma, and the survival rate of patients with recurrent disease remains especially poor. Evolutionary pressures, such as chemotherapy exposure, acting on a diverse population of cancer cells selects for subclones with a fitness advantage over other cells, driving the progression toward drug resistance. As poor survival rates are largely attributable to resistance to standard chemotherapy, there is an unmet need to elucidate the fitness bottlenecks present along the path to chemoresistance and means by which to overcome it. We adapted the previously described Genome Editing of Synthetic Target Arrays for Lineage Tracing (GESTALT) approach to investigate the evolutionary trajectories of osteosarcoma cells during the acquisition of doxorubicin resistance.

Methods: Via lentiviral transduction, a synthetic barcode array of ten Cas9/sgRNA targets was integrated into the genome of the 143B human osteosarcoma cell line (Fig. 1A) before transfection with a Cas9-expressing plasmid and GESTALT sgRNA. This results in a diverse accumulation of edits in the barcode region of each cell (Fig. 1B). These unique barcodes are passed down to daughter cells, thereby enabling single cell ancestry tracing. Barcoded 143B cells were then adapted to doxorubicin by chronic exposure to increasing doses of doxorubicin (Fig. 1C). In parallel, a control group of barcoded 143B cells was carried in matching doses of DMSO. Resistant cells were released from drug to create doxorubicin-released cell lines. DNA sequencing of barcodes was performed on resistant, sensitive, and released groups to query their subclonal compositions. RNA and whole exome sequencing were performed on these groups to identify gene regulatory networks important for the development of doxorubicin resistance.

Results: Creation of barcoded doxorubicin-resistant cells (DoxoR) and sensitive control cells (DoxoS) was validated, with dose-response curves showing 0% cell death in DoxoR and 87% in DoxoS (Fig. 2A). DoxoR proliferated at significantly slower rates than DoxoS ($P<0.001$, Fig. 2B). While DoxoR cells released from doxorubicin exposure for 2.5, 4, and 6 weeks remained resistant (Fig. 3A), 5-week release led to an increase in proliferation rate compared to DoxoS and 1-week release ($P<0.001$, Fig. 3B). Analysis of RNA-Seq data from these different time points revealed that, despite removal of drug, all populations maintained constant upregulation of ABC transporters and other known drug resistance genes.
DNA sequencing of barcodes revealed that the evolutionary fitness bottleneck imposed by the drug adaptation process dramatically changed subclonal composition. Two subclones that together comprised less than 0.2% of the DoxoS population together accounted for around 90% of the DoxoR population, indicating that they were better suited to survive in doxorubicin compared to other subclones (Fig. 3C). Additionally, one subclone that comprised less than 0.1% of the population in DoxoS, DoxoR, 1-week, and 2-week released lines was found to constitute nearly 40% of the population in the 4-week released line, suggesting the rise of a proliferative subclone (Fig. 3C).
An integrated RNA-Seq and exome sequencing approach identified key gene regulatory networks with druggable network nodes. Follow-up studies are testing whether these actionable nodes can be used to selectively target the highly proliferative DoxoR subclones and prolong the lives of patients with therapy-resistant osteosarcoma.

Conclusion: The GESTALT approach was used to study evolutionary fitness bottlenecks along the path to doxorubicin resistance in osteosarcoma cells. RNA-Seq and exome sequencing elucidated important gene regulatory networks and druggable nodes that could be explored for selective targeting of therapy-resistant subclones.

Figure 1. The GESTALT barcoding system was adapted for use in osteosarcoma cell lines. A) A barcode with ten Cas9 target sites (blue bars) is introduced into the genome of interest. Cas9 introduces an edit (red bar) that will be passed onto all progeny cells. **B)** The heterogeneous edited barcodes of the initial population are passed to daughter cells. **C)** The filled portion of each circle represents confluency, the percent of surviving cells at each dose. The transition from a fully confluent to a less confluent plate with the increasing dosage of doxorubicin represents a fitness bottleneck event, selecting for cells that are increasingly resistant to doxorubicin.

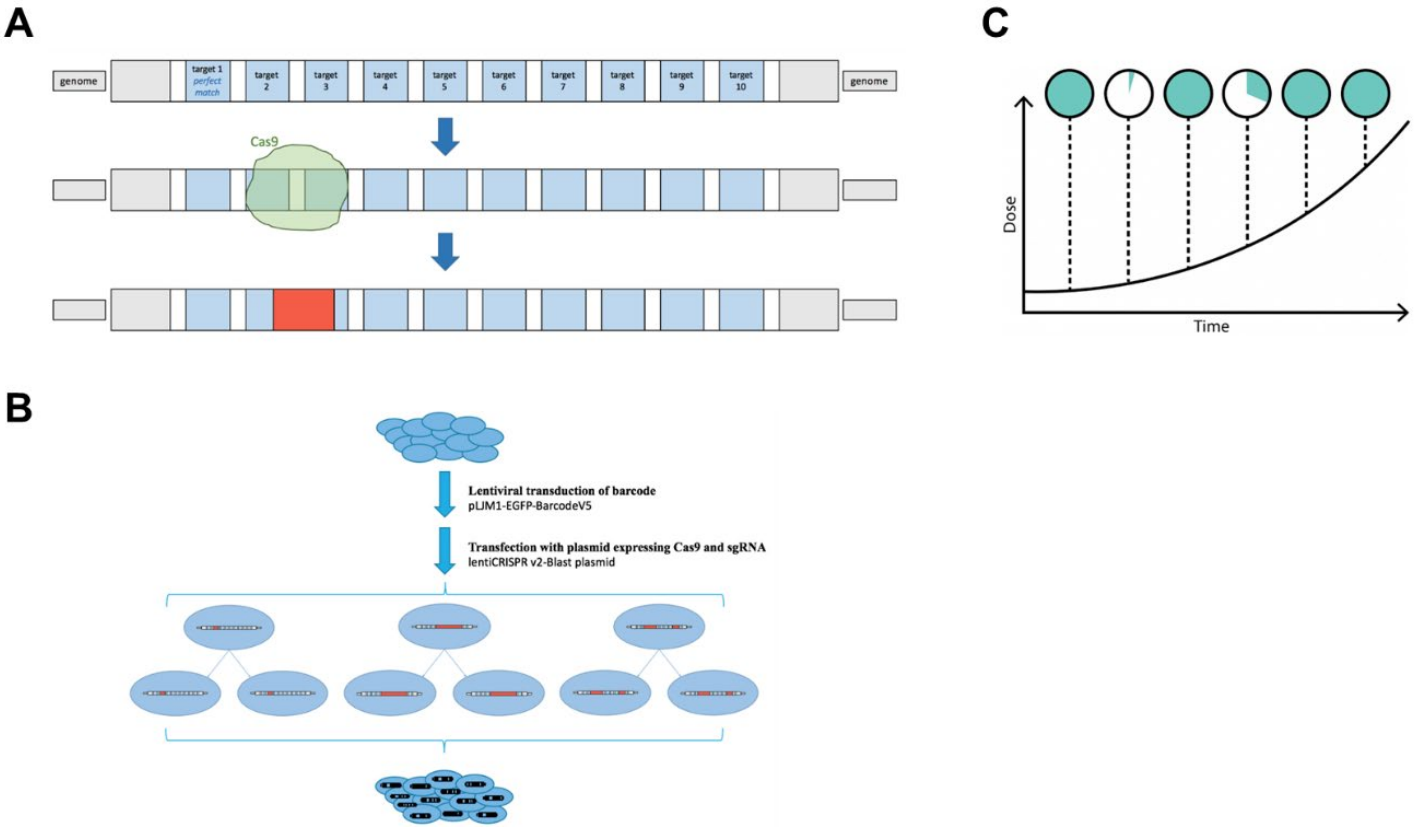


Figure 2. Doxorubicin-resistant cells were successfully produced. A) DoxoR cells were confirmed to be resistant to up to 80 nM doxorubicin. Treatment duration was 72h. B) DoxoR grew slower than DoxoS.

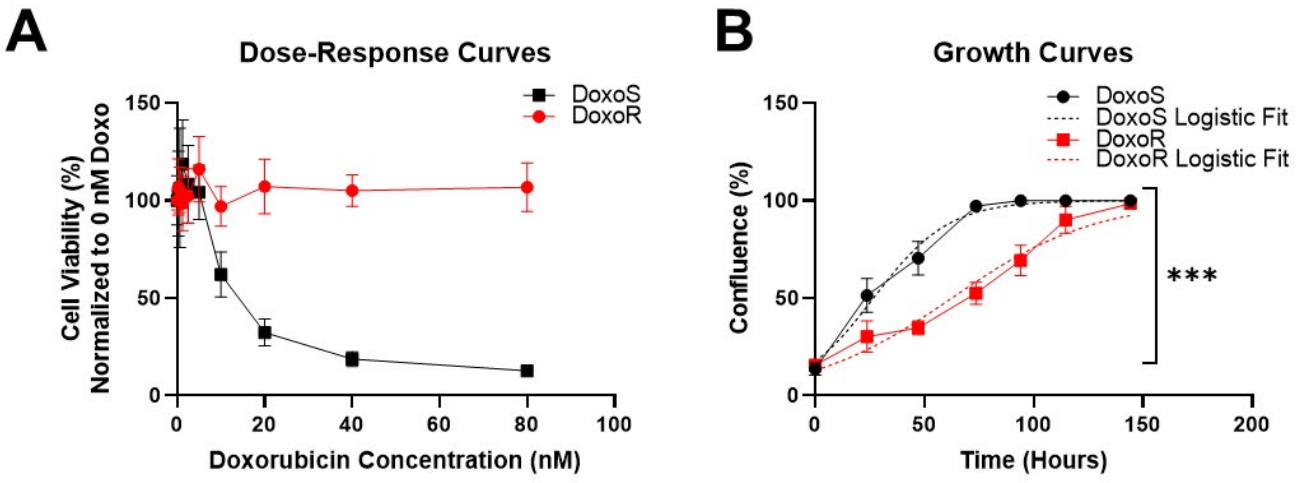
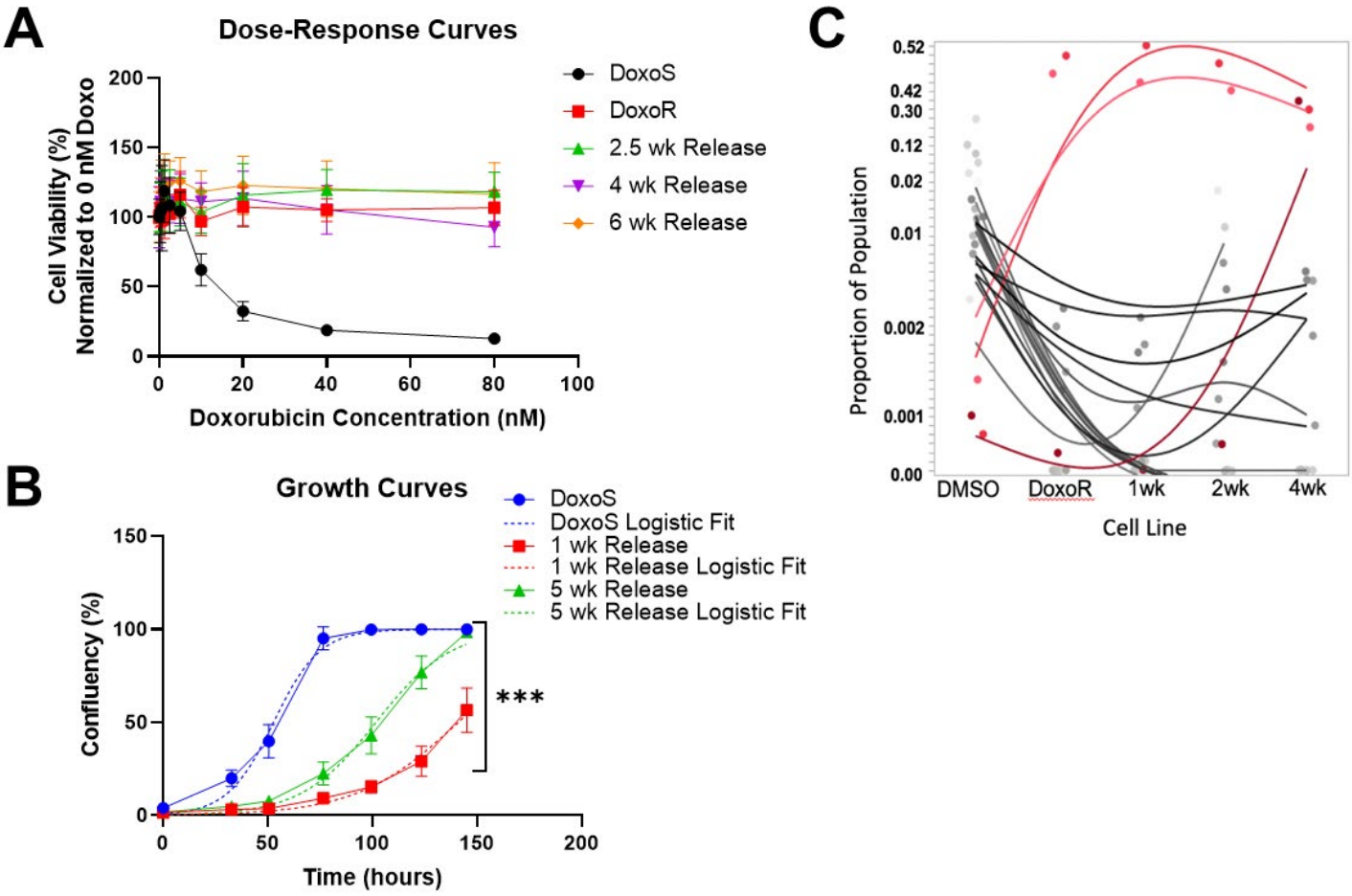


Figure 3. Key findings in resistant cells released from doxorubicin. A) DoxoR cells released from doxorubicin for several weeks retained doxorubicin resistance. B) Increased proliferation rate was observed in cells released for 5 weeks vs 1 week. C) Two subclones (light red) initially at low frequency in the DoxoS cell line predominated in DoxoR after adaptation to doxorubicin. A subclone (dark red) initially observed at low frequency rose to constitute 40% of the subclonal population between weeks 2 and 4 of release from drug.



Poster #214 3465233

ADJUNCT DIAGNOSTIC STRATEGIES IN IMPROVING DIAGNOSTIC YIELDS IN IMAGE-GUIDED BIOPSIES – A COST-EFFECTIVENESS ANALYSIS

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Objective: Routine use of adjunct intra-procedural fresh frozen biopsy (FFP) or point of care (POC) cytology at the time of image-guided biopsy can improve diagnostic tissue yields for musculoskeletal neoplasms. Potential benefits include hastened diagnoses, less repeat biopsies, and potential cost savings. The purpose of this study is to ascertain the most cost-effective adjunctive diagnostic test for image guided biopsies of musculoskeletal neoplasms.

Methods: This expected value cost-effectiveness microsimulation compared the payoffs of cost (2020 United States dollars) and effectiveness (quality adjusted life, QAL, in days) on each of the competing diagnostic strategies. A literature review, in addition to our institutional data, was used to ascertain the probabilities, diagnostic yields, utility values, and direct medical costs associated with each strategy. Payer and societal perspectives are presented. One- and two-way sensitivity analyses evaluated model uncertainties. Incremental cost-effectiveness ratio (ICER) was calculated as incremental cost per quality adjusted life day (QALD) gained and compared with standardized willingness to pay threshold of $100,000 USD.

Results: The total cost and effectiveness for each of the strategies were $1,248.98, $1414.09, $1980.53 and 80.31, 79.74, 79.69 days for the use of adjunct frozen pathology, permanent pathology only, and adjunct POC cytology, respectively. The use of adjunct frozen pathology dominated the two alternative strategies, thereby indicating that adjunct frozen pathology was less expensive and more effective than the competing alternatives. Tornado analysis revealed that the health utility of an impending diagnosis and the probability of a diagnostic result were the most influential in determining the most cost-effective strategy. One- and two-way sensitivity analyses were conducted and intra-procedural frozen pathology remained the most cost-effective strategy across all clinically plausible values.

Conclusion: The use of adjunct frozen pathology is the most cost-effective strategy in improving the diagnostic yield of image guided biopsies for musculoskeletal neoplasms. These findings are robust to one and two-way sensitivity analyses using clinically plausible probabilities.

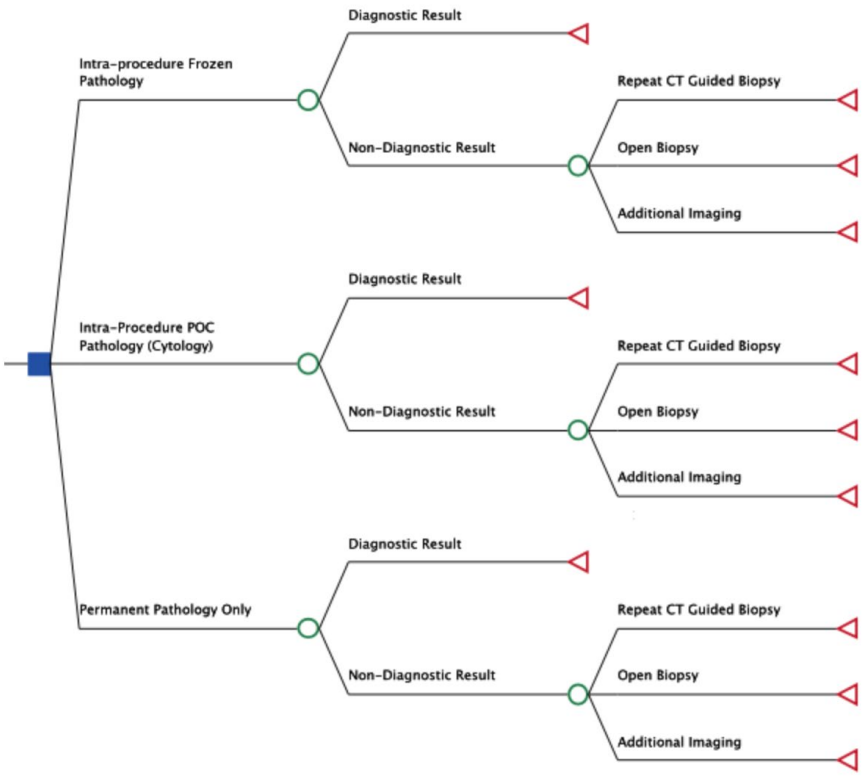

Figure 1.
Cost-Effectiveness Model Decision Tree

Poster #215 3465243

CIRCULATING TUMOR DNA IN CYTOGENETICALLY COMPLEX SOFT TISSUE SARCOMAS

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Objective: Sarcomas are rare malignancies of mesenchymal origin, accounting for approximately 1% of adult cancer diagnoses in the United States.

Sarcomas with complex cytogenetic profiles, including undifferentiated pleomorphic sarcomas (UPS), leiomyosarcomas (LMS), malignant peripheral nerve sheath tumors, dedifferentiated liposarcomas (DLPS), and liposarcomas (LPS), account for nearly 50% of sarcoma cases. These sarcomas are characterized by high genomic instability levels, manifested by frequent somatic copy number alterations (SCNAs), but they lack recurrent oncogenic single nucleotide variants (SNVs). SCNAs and SNVs are highly variable and may evolve during the patient's treatment.

Patients diagnosed with cytogenetically complex sarcomas are at high risk of developing locally advanced or metastatic disease. About half will dir of metastatic soft-tissue sarcoma within 18 months of the initial diagnosis.

Currently, diagnostic, therapeutic, and prognostic options are minimal, and there are no reliable circulating biomarkers for sarcomas. We hypothesize that circulating tumor DNA (ctDNA) will help predict response to therapy. This novel approach will identify oncogenic mutations, disease burden, and response to therapy.

Emerging data has revealed the potential use of ctDNA in LMS and GIST, among other sarcoma subtypes. One limitation is the low cfDNA content that limits analysis. Moreover, the lack of recurrent oncogenic single nucleotide variants (SNV) in cytogenetically complex sarcomas limits targeted sequencing efforts. Newer techniques such as ultra-low pass Whole Genome Sequencing (ULP-WGS) and Whole Exome Sequencing of ctDNA (ctWES) were used to detect SCNAs in ctDNA and provide a measure of the tumor fraction (TFx) of ctDNA present in blood samples.

Methods: An IRB-approved protocol was used to collect samples from 10 patients with advanced sarcomas receiving systemic chemotherapy with Doxorubicin plus Olaratumab. Blood samples were collected at regularly scheduled intervals to assess the association between TFx and genomic alterations found in ctDNA. ULP-WGS (0.1x mean coverage) sequencing was performed, and the ichorCNA algorithm was used to identify megabase-scale SCNAs from ULP-WGS data in which ctDNA comprises as little as 3% of the total cell-free DNA extracted from a plasma sample.

Results: Five patients with LMS, three patients with LPS, and two patients with UPS were included. Eight patients had serial samples over time. ctDNA was detectable in 5 of the five subjects with LMS, 2 of the three subjects with LPS, and 1 of the two subjects with UPS. (Table 1) At the first time point (cycle 1, day 1), 80% of patients had a detectable tumor fraction. However, tumor fractions were low, ranging from 0.00-5.60%. The clinical outcomes for each patient are reported. (Figure 1)

Conclusion: This pilot study shows that detecting ctDNA by ULP-WGS is feasible in cytogenetically complex sarcomas. Though tumor fractions are low, 80% of patients had detectable ctDNA on C1D1. The small sample size limited the strength of the correlations of tumor fraction with treatment response. More extensive studies are needed to optimize ULP-WGS of ctDNA for clinical use.

Figure 1.

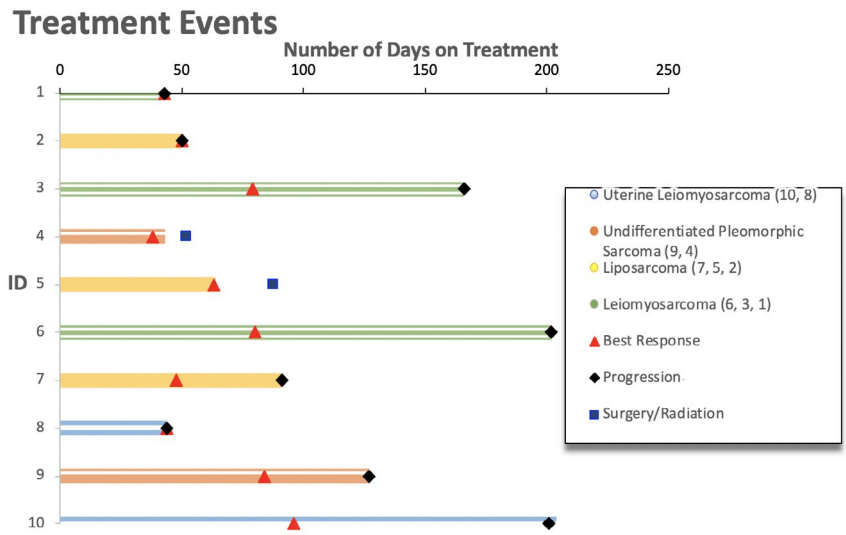

Figure 1. Swimmers plot showing tumor histology and response to treatment over time for each patient.

Table 1

ID	Age	Gender	Race	Diagnosis	Tfx C1D1	Tfx C2D1	Tfx C4D1	Tfx C6D1	Tfx C8D1
1	48	F	Caucasian	LMS	3.20%	0.61%		3.28%	
2	53	M	Caucasian	LPS	5.60%	2.59%		0.00%	
3	74	F	Caucasian	LMS	3.00%	3.85%	1.47%		
4	78	M	Caucasian	UPS	3.50%		1.35%	2.52%	
5	64	M	African-American	LPS	4.60%				
6	61	F	Caucasian	LMS	3.60%	0.00%	2.30%	1.81%	
7	65	F	Caucasian	LPS	0.00%				
8	52	F	Native American	LMS	4.30%	4.20%			
9	67	F	Caucasian	UPS	0.00%		1.14%	0.00%	3.42%
10	57	F	Caucasian	LMS	3.20%	3.19%	3.29%	1.18%	3.41%

Table 1. Patient demographics and tumor fractions

Poster #216 3465258

EVALUATION OF PATIENT AND HEALTHCARE PROVIDER KNOWLEDGE, ATTITUDES, AND BEHAVIOR (KAB) FOR SAFETY AND USE OF PEXIDARTINIB

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Objective: Pexidartinib, a kinase inhibitor, is approved in the US for treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery. Due to potential hepatotoxicity, pexidartinib is only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) Program. As part of the REMS, a quantitative survey of Knowledge, Attitudes, and Behavior (KAB) survey was conducted. The objective of the KAB evaluation is to document the level of knowledge and assess the attitudes and behavior of patients/caregivers and healthcare providers (HCPs) regarding the following key risk messages (KRM): Pexidartinib can cause serious and potentially fatal liver injury (KRM1); monitoring of liver tests is required prior to and during treatment with pexidartinib and HCPs must withhold, modify, or discontinue the dose based on the liver tests (KRM2); and HCPs must counsel patients on the risk of serious and potentially fatal liver injury, liver test monitoring prior to and during treatment with pexidartinib, and to report any signs and/or symptoms of liver injury during therapy (KRM3; HCPs only).

Methods: The survey was administered (08Apr-07Jun2020) across 3 modalities: internet, telephone, and paper. Patients ≥18 years (caregiver participation was permitted) prescribed pexidartinib and HCPs certified in the REMS were eligible for participation. A number of controls (e.g., standardized script) were put in place to ensure the survey was conducted in a professional manner and to minimize bias. Data were analyzed descriptively.

Results: Respondents were self selected since they voluntarily responded to the invitation to participate in the survey. As of the data cut-off, 40 patients (including 1 caregiver) and 18 HCPs completed the survey. Of the 40 patients, the majority (55%) were 40-59 years, 30%/70% were male/female, 70.0% were white; and 73.7% had been receiving pexidartinib for 1-6 months. Among patients, 87.5% demonstrated understanding of KRM1, 87.5% demonstrated understanding of KRM2, and 77.5% demonstrated understanding of both KRMs by meeting or exceeding the 80% knowledge threshold (Table 1). HCPs were 66.7%/27.8% male/female and included medical doctors (77.8%), advanced practice nurses (16.7%), and physician assistants (5.6%) specializing in oncology (77.8%) or orthopedics (22.2%). Most (72.2%) reported having prescribed pexidartinib ≤3 months prior to participation. Among HCPs, 83.3% demonstrated understanding of KRM1, 88.9% demonstrated understanding of KRM2, 100% demonstrated understanding of KRM3, and 83.3% demonstrated understanding of all 3 KRMs (Table 1).

Conclusion: The KAB survey demonstrated that both patients prescribed pexadartinib and HCPs prescribing pexidartinib to patients with TGCT have a good understanding of the KRMs, indicating that the pexidartinib educational goal of REMS is effective. The knowledge acquisition is expected to support the REMS in the mitigation of the risk of serious and potentially fatal liver injury. This is by ensuring patients and HCPs are informed about the risks associated with the use of pexidartinib and the requirement for baseline and periodic monitoring during treatment.

Table 1. Demonstrated Understanding of Pexidartinib Key Risk Messages

	Patients (N=40) a n (%) [95% CI] b	HCPs (N=18) a n (%) [95% CI] b
Demonstrated understanding of KRM1	35 (87.5) [76.9-93.6]	15 (83.3) [57.5-94.9]
Demonstrated understanding of KRM2	35 (87.5) [76.9-93.6]	16 (88.9) [63.0-97.4]
Demonstrated understanding of KRM3 c	--	18 (100.0) [81.5-100.0]
Demonstrated understanding of 0 KRMs	1 (2.5)	0
Demonstrated understanding of 1 KRM	8 (20.0)	2 (11.1)
Demonstrated understanding of 2 KRMs	31 (77.5) [65.6-86.1]	1 (5.6)
Demonstrated understanding of 3 KRMs c	--	15 (83.3) [57.5-94.9]

KRM = Key Risk Message
Patient; KRM1 = TURALIO can cause serious liver problems, which may be severe and can lead to death.; KRM2= It is important for patients to have blood testing performed to check their liver health before starting and while taking TURALIO.
HCP = healthcare provider; KRM1= Pexidartinib can cause serious liver problems which may be severe and can lead to death.; KRM2= It is important for patients to have blood testing performed to check their liver health before starting and while taking pexidartinib.;KRM3= HCPs must counsel patients on the risk of serious and potentially fatal liver injury, liver test monitoring prior to and during treatment with pexidartinib, and to report any signs and/or symptoms of liver injury during therapy.
Note: A respondent is counted as having demonstrating understanding if he/she correctly answered 80% or more of the questions/items in each key risk message.
a Total number of eligible respondents completing the survey.
b Logit-transformed CIs were used to take into account the finite population. Clopper-Pearson CIs were used for proportion estimates of 0 and 100.
c KRM3 was appropriate for HCPs only.

Poster #217 3465259

PATIENT-DERIVED SARCOMA MODELS TOWARDS NOVEL BIOLOGY AND TREATMENT

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Objective: This study aims to establish patient-derived sarcoma cell lines and xenografts as fundamental research resource for novel biology and innovative medial seeds. A paucity of adequate patient-derived models is one of the factors to hinder the research progress and the treatment development in sarcomas. We tackle this issue by establishing novel models.

Methods: The surgically resected tumor tissues were obtained from the patients with sarcomas, who visited the National Cancer Center Hospital or Tochigi Cancer Center Hospital. The patient-derived cell lines and xenografts were established from the tumor tissues. In brief, the tumor tissues were mechanically and enzymatically dissected and maintained in the tissue culture conditions. The mechanically dissected tumor tissues were subcutaneously inoculated to the immune-deficient mice. The spontaneously growing tumor cells were authenticated by examining STR profile and searching the database, Cellosaurus. The status of fusion genes and copy number variations were examined for all established models. The cells were subjected to the characterization such as the capability of growth, spheroid formation, and invasion. The anti-proliferative effects of more than 200 anti-cancer agents, which were approved for the treatments of other malignancies or the investigational ones, were examined by the automated liquid handling machine. Target NGS was performed to identify the status of actionable genes using NCC Oncopanel. Proteomic analysis was performed using mass spectrometry and PamStation. This study was approved by the ethical committee of National Cancer Center and Tochigi Cancer Center, and the informed consent was obtained from the patients or their parents who participated in this study.

Results: Tumor tissues of more than 360 sarcoma cases were examined in this study, and a total of 45 cell lines and 40 xenografts were established from sarcomas with different histology. Those included the extremely rare sarcomas such as alveolar soft part sarcoma, CIC-rearranged sarcoma, and MPNST of bone. All established models possessed the identical fusion genes with their original tumors, or the aberrant genomic backgrounds close to those of their original tumors. All established cell lines formed spheroids when they were placed on the ultra-low attachment substrates. The drug screening identified anticancer agents, whose efficacy was not previously reported in sarcomas. The relationship between the status of actionable mutations and the response to molecular targeted drugs in the models is under investigation. Integration of genomics and proteomics data will also be our next challenge, and we generated an original sotware for this purpose.

Conclusion: We established patient-derived sarcoma models such as cell lines and xenografts using surgically resected tumor tissues from patients with sarcomas. The correlation between the response to treatments with anticancer agents and the genetic and proteomic backgrounds is under investigation. The established cell lines were reported in the academic papers, and delivered to the researchers upon their requests. The established cell lines and xenografts are used for the collaboration with the researchres in the academic institutes or the for-profit companies. We will continue the model establishment using tumors from additional sarcoma cases. We are planning to establish the domestic and international multi-institutional collaboration about the establishment and application of patient-derived sarcoma models. Your interest to our models and participation to our research activity are very welcome.

Poster #218 3465280

OUTCOMES OF WOUND HEALING WITH A TOPICAL SKIN ADHESIVE AFTER TUMOR RESECTION

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Objective: Cyanoacrylate topical skin adhesives are routinely used to close surgical wounds. Prior studies have noted an antibacterial effect of the skin adhesives in addition to a decreased risk of post-operative wound drainage and equivalent to decreased rate of post-operative complications compared to staple or nylon closure. Currently, there is no report in the literature regarding use of topical skin adhesives after musculoskeletal tumor resection. The purpose of this study is to evaluate the outcomes of wound closure with a topical skin adhesive.

Methods: A retrospective chart review of all patients who underwent surgical resection of a bone or soft tissue tumor was performed. A layered closure with a subcuticular monofilament suture followed by a cyanoacrylate topical skin adhesive was used in all cases. It has become the standard at our institution to use a topical skin adhesive for closure except for when the patient had undergone neoadjuvant radiation to the area within a year. Only primary closures were included, and all delayed closures, patients presenting with fungating tumors, or those treated with a skin graft or free flap were excluded. Demographics, type of tumor removed, comorbidities, size of the resected specimen based on pathology reports and wound complications within six months of surgery were evaluated. Wound complications were subdivided into whether intervention was required (antibiotic treatment, dressing changes, operative debridement, etc.) or no intervention was required (superficial dehiscence, asymptomatic seroma, etc.). Complications requiring operative debridement were also evaluated separately.

Results: A total of 241 patients were included for review. A full set of demographics and risk factors are included in Table 1. Younger age (p=0.04), higher body mass index (p=0.027), length of the resected specimen (p=0.002) and volume of the resected specimen (p=0.039) were associated with an increase in overall complications. Resection of a high-grade sarcoma approached significance (p=0.055). Patients with metastatic disease were less likely to have a wound complication (p=0.047, OR 0.31). Complications occurred in 36 (14.9%) of patients, with 20 (8.3%) requiring an intervention and 7 (2.9%) requiring operative debridement (Table 2). Complications after bone tumor resection were more likely to require operative debridement compared to soft tissue tumors (p=0.0049). Patients who returned to the operating room were also more likely to have a high-grade sarcoma and undergone adjuvant and neoadjuvant chemotherapy.

Conclusion: A prior study evaluating staple versus nylon suture closure in musculoskeletal tumor surgery noted a 5% wound complication rate with staples, 11% with nylon, and an overall complication rate of 5.5%. It is notable that the criteria for a wound complication in this study was hospitalization within 6 months due to the wound, antibiotic treatment, or operative debridement. If these criteria are applied to this study, 8 (3.3%) patients sustained a wound complication with only 7 (2.9%) requiring operative debridement. Similar to the literature, a higher body mass index and larger tumor size were associated with complications. Overall, wound closure with a topical skin adhesive provided a low risk of returning to the operating room and should be considered as a viable method of skin repair in musculoskeletal tumor surgery.

Table 1: Demographics and risk factors

Variable	No complication group* (N=205)	Complication group* (N=36)	Significant P-values
Age	47.9 ± 22.91 (6 to 90)	39.4 ± 22.2 (9 to 85)	0.04
Sex			
Male	111	15	
Female	94	21	
Body Mass Index	27.6 ± 7.15 (13.2 to 44.9)	31.0 ± 8.3 (14.9 to 52.2)	0.027
Drain placed	92	22	
Diabetic	22	1	
Smoker	11	3	
Neoadjuvant chemotherapy	52	11	
Adjuvant chemotherapy	71	14	
Neoadjuvant radiation	5	1	
Adjuvant radiation	61	6	
High-grade sarcomas	62	17	0.055†
Low-grade tumors	25	7	
Benign tumors	71	9	
Metastatic cancer	47	3	0.047 0.31 (0.09 to 1.04)‡
Bone tumors	87	13	
Soft tissue tumors	118	23	
Megaprosthesis or intercalary allograft	19	2	
Length of specimen (cm)	9.2 ± 5.9 (1 to 30)	16.7 ± 9.0 (2 to 42)	0.002
Volume of specimen (cm^3)	417.0 ± 806.9 (0.15 to 5095)	1167.4 ± 2081 (0.8 to 11880)	0.039

*The values are given as the mean and the standard deviation with the range in parentheses for continuous variables and as the number of patients with the percentage of the total in parentheses for all categorical variables. †Nearing significance. ‡Odds ratios are given for significant categorical values. 95% confidence intervals are given in parentheses.

Table 2: Complications

Complications in detail	Bone tumors (N=13)	Soft tissue tumors (N=23)	Total (N=36)
Minor wound breakdown with no intervention needed	3	4	7
Wound drainage not requiring intervention	2	1	3
Seroma not requiring intervention	0	5	5
Seroma requiring aspiration	0	1	1
Suture abscess	0	1	1
Cellulitis requiring antibiotics	0	1	1
Superficial breakdown treated with silver sulfadiazine	2	2	4
Wet-to-dry dressing changes required	0	3	3
Rash treated with removal of the adhesive and diphenhydramine	0	4	4
Operative debridement required	6	1	7 (0.0049)

Significant p-values are noted in parentheses

Poster #219 3465283

A NEW INDUCIBLE ZEBRAFISH MODEL OF EWING SARCOMA REVEALS THE IMPORTANCE OF ECM IN DEVELOPMENT OF THE DISEASE

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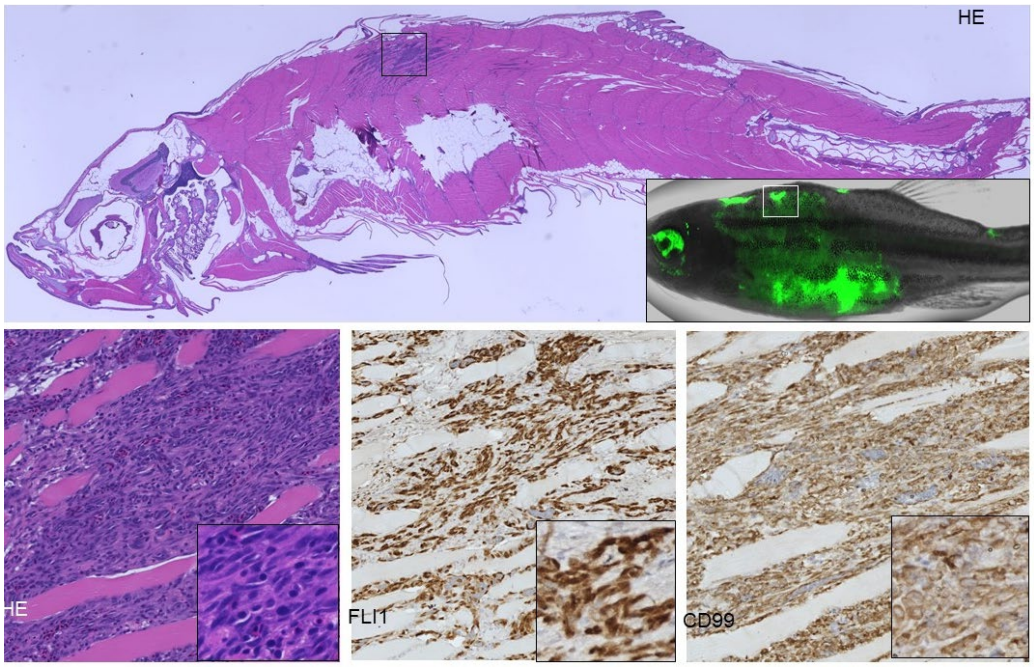
Objective: The Ewing sarcoma family is a group of malignant small round blue cell tumors that affects children and young adults. The tumors are characterized by the presence of one of several chimeric fusion proteins, most frequently EWSR1-FLI1. Survival is extremely poor for patients with metastatic or relapsed disease. Attempts to develop molecularly-targeted therapies for Ewing sarcoma have been very challenging, owing to the difficulty of targeting the oncofusion. Progress in the field is slowed by the absence of a reliable animal model of the disease.

Methods: To optimize the EWSR1-FLI1 expression in zebrafish we have tested several tissue-specific and ubiquitous promoters to drive the oncofusion expression in embryos. We integrated constructs one by one into the zebrafish genome using a tol2-based approach. Zebrafish were injected at the single-cell stage. To confirm the expression of EWSR1-FLI1 in GFP positive zebrafish embryos or tumor tissues, we performed RT-PCR and Western blot analysis.
Zebrafish with tumors were euthanized and screened under a Nikon SMZ25 fluorescent stereomicroscope to detect the GFP indicative of transgene expression. Fish with tumors were placed in histology cassettes and fixed in 4% paraformaldehyde (1xPBS) for 48 h followed by the de-calcification in 0.5M EDTA for 5 days. Tumor specimens were mounted in paraffin blocks for microtome sectioning. Hematoxylin and eosin staining as well as CD99, EWSR1-FLI1 immunostaining were performed on de-paraffinized slides.

Results: Cre-inducible expression of EWSR1-FLI1 oncofusion in zebrafish embryos was confirmed on both RNA and protein levels. The oncogene drives high-incidence tumor development in the first 3 months. Immunostaining reveals that the tumors are positive for EWSR1-FLI1 and CD99, a known Ewing sarcoma marker. We found that EWSR1-FLI1 expression deregulates the profile of protein expression in developing embryos, affecting normal cell differentiation.

Conclusion: We have developed a new efficient zebrafish model of Ewing sarcoma which allows the Cre-inducible expression of EWSR1-FLI1 fusion in zebrafish. The advantage of the model is the possibility to study tumor initiation and progression in specific developmental contexts. New findings reveal the importance of extracellular matrix and proteoglycan metabolism in the development of EWSR1-FLI1-driven Ewing sarcoma.



Poster #220 3465290

SQ3370-001: A MULTI-CENTER, OPEN-LABEL PHASE I DOSE-ESCALATION STUDY OF SQ3370, A NOVEL INTRATUMORAL AND SYSTEMIC APPROACH TO ADMINISTER ANTHRACYCLINES FOR TREATING SOFT TISSUE SARCOMAS AND OTHER ADVANCED SOLID TUMORS

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Objective: Anthracyclines are regarded as the first-line treatment of choice for soft tissue sarcoma (STS) and other solid tumors. However, objective responses are uncommon and risks of cardiotoxicity limit treatment to a maximum of 4-5 months. In this first-in-human (FIH) Phase 1 study, we are evaluating the safety and tolerability of SQ3370, a novel treatment approach that involves local intratumoral injection of a prodrug-capturing biomaterial (SQL70) followed by 5 daily systemic infusions of an attenuated prodrug of doxorubicin (SQP33). Complementary chemical groups in the 2 components allow the local capture and release of active doxorubicin *in situ*. In pre-clinical models, this approach allowed an 8.95-fold increase in doxorubicin dosing with minimal systemic adverse events including cardiotoxicity in dogs. In addition, there was clear evidence of tumor regression in non-injected distal lesions, suggesting a systemic anti-tumor effect of the treatment. (Preclinical data is presented in a separate abstract.) The local capture and activation technology of SQ3370 is solely based on chemistry and is independent of tumor biomarkers or local factors such as enzymatic activity, pH or oxygen levels.

Methods: SQ3370-001 is a Phase I study that will enroll patients ≥ 18 years of age with an injectable local or metastatic lesion of STS or other solid tumors, for which published data indicates responsiveness to anthracyclines. Patients must be relapsed or refractory following standard of care therapy and have not received more than 225 mg/m^2 of doxorubicin (or equivalent anthracycline). Treatment cycles will be 21 days long with no limit on total cycles. Dose escalation will follow an accelerated titration design and then switch to a 3+3 design. The starting human dose of SQP33 prodrug with a fixed volume of SQL70 biomaterial was determined in accordance with ICH S9 guidelines, which propose using 1/6th of the human equivalent dose highest non-severely toxic dose (HNSTD) seen in a GLP toxicology study in dogs (the relevant species for doxorubicin).

Results: The primary objective will be to assess the safety and tolerability of SQ3370 and to determine the recommended Phase 2 dose (RP2D). Secondary objectives include characterizing the pharmacokinetic profile, assessing preliminary signals of anti-tumor activity per RECIST 1.1 and immune responses. This study is expected to enroll up to 40 patients.

Conclusion: SQ3370 represents a new therapeutic modality to treat STS and other solid tumors by using a drug with known efficacy, doxorubicin, and expanding its pharmacological capabilities while minimizing its systemic toxicity. Further, SQ3370's systemic anti-tumor effect could greatly benefit patients with widely disseminated or undetectable micro-metastatic lesions. This FIH study will validate the local capture and activation technology, and in the future, could be applied to a variety of cytotoxic drugs that have been limited by their systemic toxicity. **SQ3370-001 is open to enrollment in the United States and Australia.**

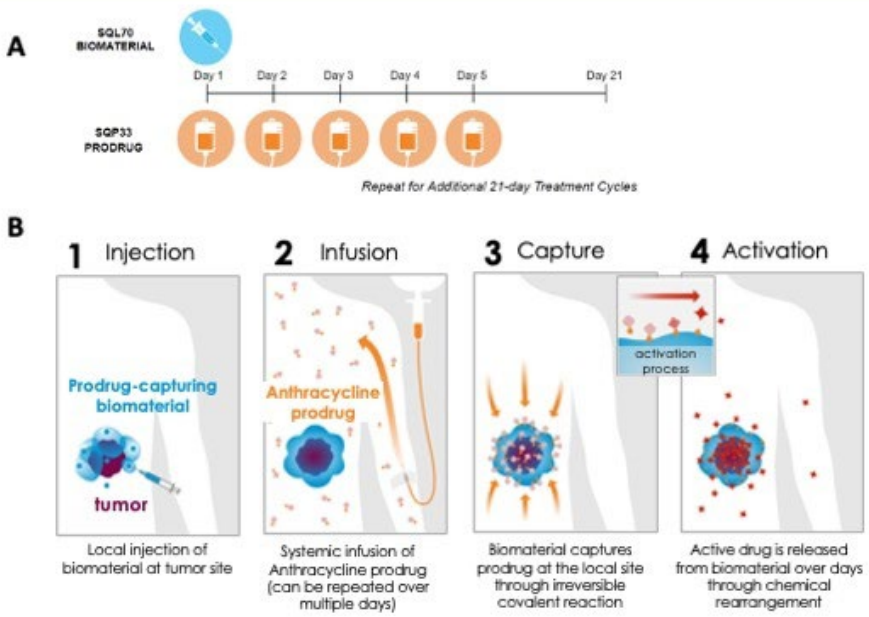

Figure 1. SQ3370 Investigational Product. (A) Treatment cycle and (B) Mechanism of Local Capture and Activation.

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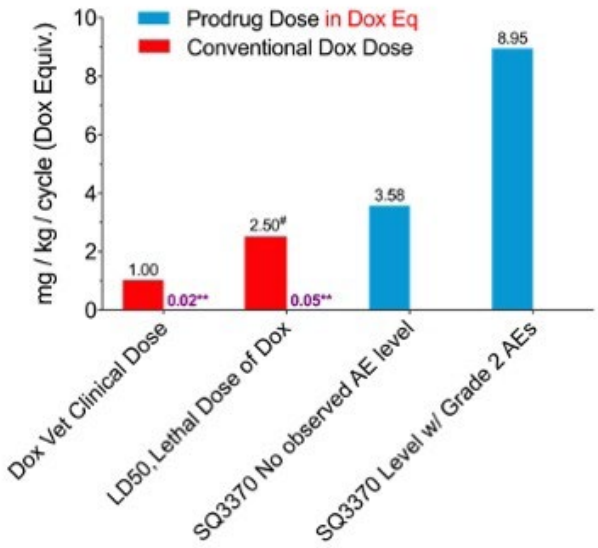
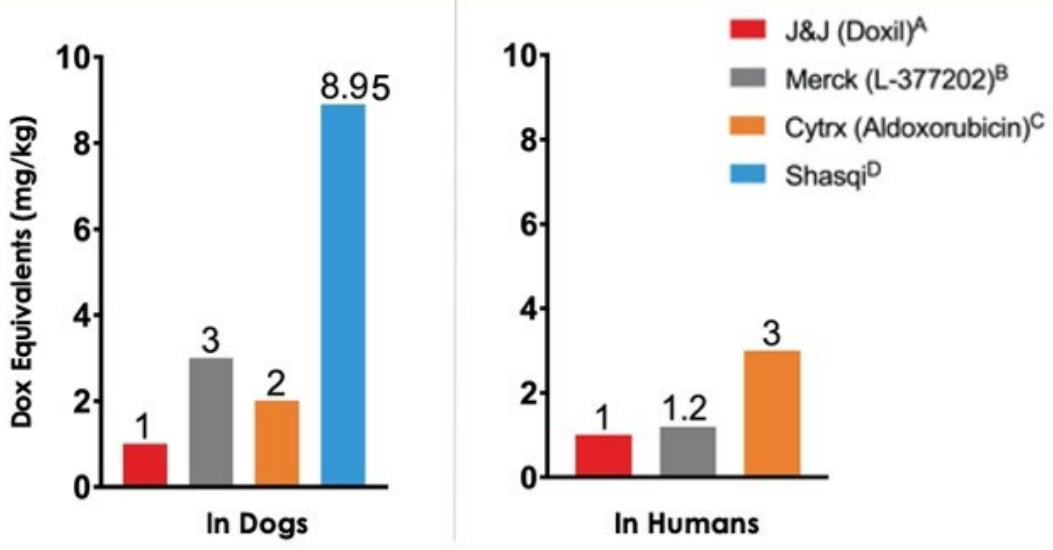


* Doxorubicin exposure to tumor,
* C. Bertazzoli et. al. Toxicol. Appl. Pharmacol, 1985; 79:412-422.
** C. Li et. al. J. Nuc. Med. 1997, 38, 1042 - 1047
ζ Grade 2 AE level corresponds to highest non-severely toxic dose (HNSTD)
Dox Eq = Doxorubicin equivalents

Figure 2. Dose Comparison of SQ3370 with Conventional Doxorubicin in Dogs (GLP Toxicology)



Dose per Cycle Resulting in ≥ Grade 2 Side Effects

Sources -
A: Working *et. al.* Hum Exp Toxicol, **1996**, 15, 751-85. **B:** DeFeo-Jones *et. al.* Mol Cancer Therap. **2002**, 1, 451-459; DiPaola *et. al.* J Clin Onc. **2002**, 20, 1874-1879.
C: Kratz *et. al.* Human & Exper Toxicol, **2007**, 26, 19-35; Unger *et. al.* Clin Cancer Res, **2007**, 13, 4858-4866. **D:** Unpublished results.

Figure 3. Dose Comparison of SQ3370 with other Doxorubicin approaches.

Poster #221 3465303

PEDIATRIC ONCOLOGY PROVIDERS' MENTAL HEALTH IN THE EPICENTER OF THE PANDEMIC, PRELIMINARY REPORT

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Objective: Covid-19 has had monumental effects on patients and healthcare workers worldwide. Though cases are now starting to decrease in many states, other states are once again starting to see more cases. Since the outbreak, doctors and nurses have reported drastic increases in mental health issues such as depression, anxiety, sleep disturbances, self-reported stress levels, and more. Fear of contacting the virus, especially fear of transmitting COVID-19 to loved ones and to vulnerable patients add to the mental toll on providers. Pressure to be "heroic," is exacerbated by intense scrutiny from the public and the media. There is not yet research focusing on pediatric providers, called upon to work during the pandemic. The increased burden of long hours, struggles with PPE, and no knowledge of who may be infected, can make overworked providers more prone to mental fatigue, especially when caring for the most susceptible patients, like those with cancer, who cannot miss or delay treatment. The uncertainty of working in the midst of the pandemic can be disastrous for providers and it is important to recognize and acknowledge these issues.

Methods: We created an exploratory survey to be passed out in the Pediatric care units (regular floor, clinic, PICU) at two hospitals that saw the largest peak COVID cases in Cook County (up to 350 a day) in one of the National Hot-spots. This anonymous survey helped to gauge how providers are feeling mentally and emotionally pertaining to COVID-19. Ten statements self-scored on Likert scale were answered, with "1" being the least relatable to "5" being the most relatable.

Results: There were 54 participants total, 40 from the Rush, 14 from the University of Illinois at Chicago (UIC) hospital. Of those surveyed, 43 were female and seven were male. In all, 59% identified as White/Caucasian. Physicians made up 33% of respondents, ten from Rush and seven from UIC. Nurses made up 56% of respondents total. Other participants included three medical students, one nurse practitioner, one advanced practice nurse, and one child life specialist from Rush. Most participants were between the ages of 26 and 29, 76% of them aged 35 and under.
Most participants expressed feelings of anxiety and depression. Overall 37% of participants rated the statement pertaining to anxiety at a "4." Feelings of depression were slightly more common with 43% of the participants, ranking these feelings at a "4" or a "5." Feelings of exhaustion, burnout, and emotional distress were most prevalent within 61% of participants.

Most workers expressed fears of transmitting the virus, with 63% of them expressing concern over transmission to themselves or their families, and 60% expressing fear over transmission to patients. In 24% of providers, these feelings worsen as the pandemic goes on. Many providers reported feeling more pressured in the workplace at 40%, though most providers expressed little to no concern about extra workplace demands. UIC providers reported feeling slightly more pressured than Rush (P=0.544), as well as feeling more of a need to appear emotionally unaffected at work (P=0.462).

Conclusion: The Covid-19 can heavily impact providers even in fields that may not encounter as many Covid-19 patients as others. Negative feelings pertaining to the pandemic were found to prevail through all types of providers surveyed. Feelings of burnout and exhaustion were the most prevalent across both hospitals, which could be detrimental to providers and patients. In addition to poor mental health, there are providers expressing feelings of not being "equipped to keep [myself] or [my] patients safe." Though this is not the majority of providers, this can still be an important issue to be addressed. This study not only provides insight into how providers are emotionally and mentally coping with the struggles of the pandemic, but also brings into light notable differences in between the two hospitals. Further research is needed in order to look deeper into the reasons why.

UIC Data

Age	Participants	Gender	Participants	Ethnicity	Participants	Title	Participants
20-25	0	Male	2	White/Caucasian	5	Physician	7
26-29	6	Female	11	Hispanic	4	Nurse	7
30-35	3	Prefer not to answer	1	Asian	2		
40-44	1			Black/ African American	3		
45-50	1						
50-55	2						
Unknown	1						

Statement	Ranking				
	5	4	3	2	1
	Number of Participants:				
Since the start of the Covid-19 pandemic, I find that I am more worried or anxious about coming into work.	4	4	3	2	1
Since the start of the Covid-19 pandemic, I find that I feel more sad or more depressed than usual.	3	5	4	0	2
Since the Covid-19 outbreak, I find that I am experiencing more feelings of exhaustion, burnout, and/or emotional distress.	5	7	1	0	1
I am scared of contracting the Covid-19 virus myself or to my family.	5	3	1	3	2
I am scared of transmitting the Covid-19 virus to my patients.	3	8	3	0	0
I worry that I am not equipped well enough to keep myself or my patients safe.	0	0	5	6	3
I feel that my personal fears regarding the Covid-19 pandemic has affected the way that I treat patients.	1	0	2	5	6
The longer the pandemic goes on, the more anxious, depressed, stressed, scared, etc. I feel.	0	3	5	5	1
I have felt extra pressure at work.	5	2	0	2	3
It is important to me that I maintain an appearance of not being emotionally affected by this pandemic.	2	4	4	0	4

Rush Data

Age	Participants	Gender	Participants	Ethnicity	Participants	Title	Participants
20-25	4	Male	6	White/Caucasian	27	Physician	11
26-29	19	Female	34	Hispanic	2	Nurse	23
30-35	9			Asian	7	Nurse Practitioner	1
36-40	2			Native Hawaiian/		Advanced Practice	1
45-50	0			Other Pacific Islander	1	Nurse	
50-55	2			Black/African American	3	Medical Student	3
56+	2					Child Life Specialist	1
Unknown	2						

Statement	Ranking				
					1
	Number of Participants:				
Since the start of the Covid-19 pandemic, I find that I am more worried or anxious about coming into work.	2	16	10	9	3
Since the start of the Covid-19 pandemic, I find that I feel more sad or more depressed than usual.	2	13	13	3	10
Since the Covid-19 outbreak, I find that I am experiencing more feelings of exhaustion, burnout, and/or emotional distress.	6	15	9	6	4
I am scared of contracting the Covid-19 virus myself or to my family.	13	14	6	5	1
I am scared of transmitting the Covid-19 virus to my patients.	11	11	9	5	4
I worry that I am not equipped well enough to keep myself or my patients safe.	1	4	8	14	13
I feel that my personal fears regarding the Covid-19 pandemic has affected the way that I treat patients.	0	2	10	13	15
The longer the pandemic goes on, the more anxious, depressed, stressed, scared, etc. I feel.	5	8	7	14	6
I have felt extra pressure at work.	7	7	10	9	7
It is important to me that I maintain an appearance of not being emotionally affected by this pandemic.	7	9	3	12	9

Poster #222 3465305

A META-ANALYTIC EVALUATION OF THE CORRELATION BETWEEN SURROGATE ENDPOINTS AND OVERALL SURVIVAL IN RANDOMIZED CONTROLLED TRIALS OF NEWLY DIAGNOSED OSTEOSARCOMA

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Objective: Event-free survival (EFS) is considered the most reliable surrogate endpoint for overall survival (OS) in randomised controlled trials (RCTs) of treatments for malignant tumours. However, the surrogacy of intermediate endpoints such as EFS for OS in trials of patients with osteosarcoma has not been evaluated to date. In this study, we investigated the correlation between OS and intermediate endpoints in RCTs of newly diagnosed osteosarcoma.

Methods: A systematic search identified 20 relevant RCTs. The correlations between the surrogate endpoints and OS were evaluated using weighted linear regression analyses and by calculating the Spearman rank correlation coefficients (ρ). The strength of the correlation was determined by calculating the coefficient of determination (R^2).

Results: A total of 5,620 patients were randomly assigned to 45 treatment arms in the eligible 20 RCTs. The correlation between the hazard ratios for EFS and OS was moderate (R^2 = 0.456, ρ = 0.440); this correlation tended to be weaker for patients with localised osteosarcoma excluding the patients with metastases.

Conclusion: Overall, the trial-level correlation between the surrogate endpoints and OS was not robust in RCTs of osteosarcoma published to date. Hence, the suitability of the intermediate endpoints as surrogates for OS could not be confirmed.

Poster #223 3465320

IMMUNE-CHECKPOINT GENES AS PREDICTIVE BIOMARKERS OF TRABECTEDIN IN ADVANCED SOFT-TISSUE SARCOMA (STS): A SPANISH GROUP FOR RESEARCH ON SARCOMAS (GEIS) TRANSLATIONAL STUDY

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Objective: Despite several second-line options are accessible for the treatment of advanced STS, there is a lack of predictive biomarkers available to support the rational selection of these drugs. Trabectedin specifically targets mononuclear cell lineage (macrophages and monocytes) that ultimately could inhibit tumor angiogenesis. Moreover, trabectedin seems to induce the expression of immune-checkpoint proteins (e.g. PD-L1); however, the predictive value of these factors remains unknown. The aim of this study is to analyze the potential predictive value of immune-checkpoint genes, as biomarkers of response of trabectedin in a subset of STS patients of the GEIS registry. The predictive value of *CD274*, *CD86*, *CTLA4*, *HAVCR2*, *LAG3* and *PDCD1*, and *CD163*, *CD4*, *CD68* and *CD8A* genes was analyzed.

Methods: Selection criteria included patients with STS, pretreated with at least 2 lines in the advanced setting (one line being trabectedin), with paraffin block available and ethic committee's approval. Direct transcriptomics was performed using HTG Molecular Oncology Biomarker Pathway panel (HTG Molecular Diagnostics, Inc.; Tucson, AZ, USA), following manufacturers' instructions. Data analyses were performed taking into account the median Log2 of expression of each gene and by correlating it with progression-free survival (PFS) for trabectedin, and overall survival measured from the starting date of trabectedin treatment (OS).

Results: Among 387 registered patients, fitting with the inclusions criteria, 139 cases were used for gene expression analyses, as the discovery set. Patients had median age of 52 years, 54% were females and had a median follow-up from diagnosis of 44 months. High expression of *CD274* (PD-L1) was significantly associated with better PFS of trabectedin (5.4 *vs.* 3.0 months; *p*=0.006). Similar results were obtained with high expression of *CTLA4* and *LAG3*: 6.0 vs 3.1 months; *p=0.005* and 5.4 vs 2.7 months; *p=0.042*, respectively. Expression of *CTLA4* and *LAG3* showed no significant impact in OS; whereas *CD274* high expression showed a trend towards better OS (17.9 vs 10.2 months; *p=0.077*). Also, no significant correlation was achieved for *CD163*, *CD4*, *CD68*, *CD8A*, *CD86* and *HAVCR2*; *PDCD1* (PD-1) showed a trend towards better PFS of trabectedin, *p=0.114*.

Conclusion: The expression of selected immune-checkpoint genes exhibited a potential predictive value for trabectedin in advanced STS. Validation studies (at the transcriptional and protein level) are currently ongoing to confirm their potential predictive role.

Poster #224 3465381

HETEROGENEITY OF CHEMOTHERAPY EFFECT IN HIGH-RISK PATIENTS WITH EXTREMITY SOFT TISSUE SARCOMA

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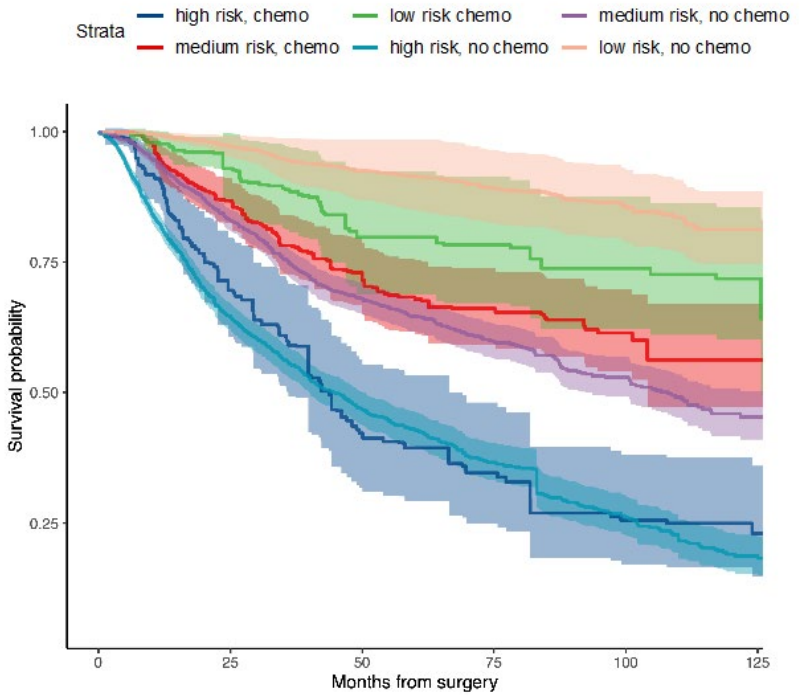
Objective: The level of evidence for perioperative chemotherapy (CTx) is primary soft tissue sarcoma of the extremities (eSTS) often debated. Recent studies suggest beneficial outcomes of perioperative CTx in a selected group of high-risk patients. Therefore, our hypothesis is that the effect of perioperative CTx differs within subgroups of patients with different baseline risk. We refer to this as heterogeneity of treatment effect (THE). The aim of this study is to identify whether heterogeneity of treatment effect of chemotherapy is present in a large cohort of patients with high-grade eSTS on 5-year overall survival (OS).

Methods: Patients with primary high-grade eSTS surgically treated with curative intent were included in this multicenter cohort study. The effect of CTx was investigated in three different OS risk groups (high risk, intermediate risk, low risk) created using the PERSARC prediction application. The risk groups were defined by the 33% and 66% quantile of these predicted 5-year OS probabilities. The effect of CTx in these risk groups was investigated using weighted Kaplan-Meier curves and a multivariable Cox proportional hazards model including an interaction term between CTx and risk groups.

Results: This study included 6505 patients with a median follow-up of 4.43 years (95% CI 4.22-4.59). The low risk group had a predicted 5-year OS of ≥76%, the intermediate risk group had a predicted 5-year OS of 57-76% and the high risk group had a predicted 5-year OS of <57% at baseline. The weighted Kaplan-Meier curves did not demonstrate a significant difference in OS between the CTx-group and no CTx-group for the high risk (p-value = 0.498) and intermediate risk patients (p-value = 0.091). However, a significant difference of OS in favor of no CTx for low risk patients was found with a p-value equal to 0.020 (figure 1). No difference in CTx effect between risk groups was found in the multivariable Cox regression model.

Conclusion: This study failed to find a beneficial effect of perioperative CTx on OS in high risk eSTS patients. Routine use of CTx should be discouraged in low risk patients and should preferably only be used in high risk patients in study context. Prediction tools, such as PERSARC, could be used to identify these high and low risk patients.

Figure 1: Weighted Kaplan-Meier curves stratified for risk group and chemotherapy treatment.



Poster #225 3465410

DEFINING A TEXTBOOK SURGICAL OUTCOME FOR PATIENTS FOR UNDERGOING SURGICAL RESECTION OF INTERMEDIATE AND HIGH-GRADE SOF TISSUE SARCOMAS OF THE EXTREMITIES

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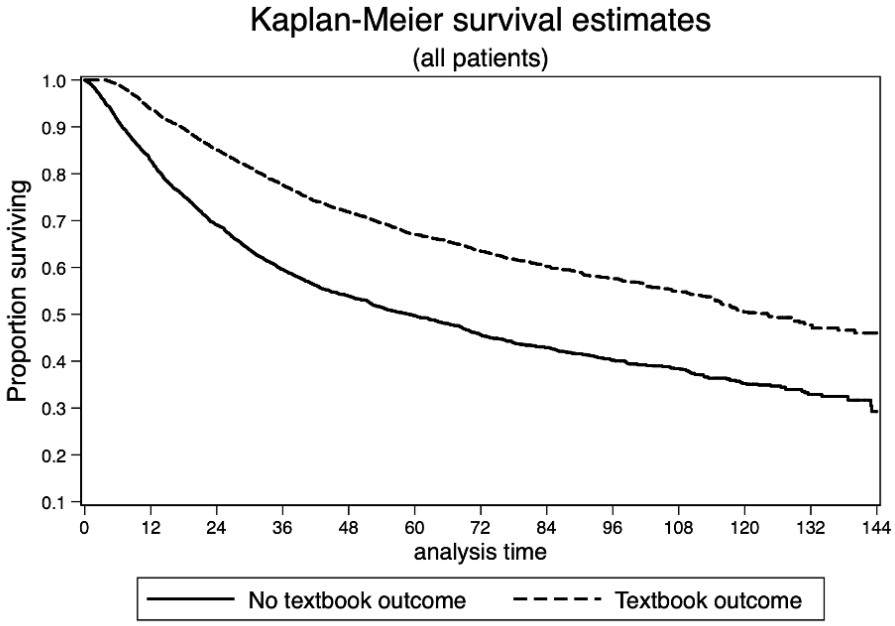
Objective: Quality measures for the surgical management soft tissue sarcoma of the extremity are limited. Emerging literature supports the concept of textbook outcomes as one novel metric to reflect multiple domains of oncologic patient care, especially in patients undergoing complex surgical procedures. Conceptually, TOs are a composite of postoperative outcomes that define the optimal "textbook" hospitalization, primarily including variables such as perioperative mortality, early postoperative morbidity, readmissions, as well as oncologic-specific variables, such as margin status and lymph node retrieval that can reflect the quality of the surgical treatment. The purpose of this study was to define a textbook surgical outcome (TO) for soft tissue sarcoma of the extremities (STS-E) and to examine its associations with hospital volume and overall survival.

Methods: All patients in the National Cancer Database (NCDB) undergoing resection of primary STS-E between 2004 and 2015 were identified. The primary outcome was a textbook *surgical* outcome, defined as: hospital length of stay <75th percentile, survival >90 days from the date of surgery, no readmission within 30 days of discharge, and negative surgical margins (R0 resection). Radiation therapy and high volume center treatment, considered key components of quality sarcoma care, were considered independent variables from our definition of a surgical TO. Modified Poisson regression was used to evaluate the independent association between a TO and patient and hospital-level factors. Non-parametric survival curves were constructed, and Cox proportional hazards regression used to determine the independent association between TO and overall survival among all patients.

Results: Overall, 7,658 patients met criteria for inclusion; a TO was achieved in 4,291 (56%) patients. Of patients who did *not* achieve TOs, 51.9% (n=1,748) had an extended length of stay, and 47.3% (n=1,591) did not have negative margins. The incidence of a TO increased over the study period across all centers. Older age, more medical comorbidities, and black, Asian or Indian race were independently associated with *not* receiving a TO (p</=0.034). Neoadjuvant radiation therapy was *not* association with likelihood of receiving a TO. With respect to tumor and treatment characteristics, larger tumor size, lower extremity location and higher grade were independently associated with *not* receiving a TO (p<0.001). Hospital volume was *not* associated with a textbook outcome. TOs conferred a significant survival benefit (HR= 0.71 [0.65-0.78], p<0.001). A TO was associated with a 27.5% longer survival time (p<0.001).

Conclusion: This large database review serves to help define a TO in the surgical management of intermediate- and high-grade soft tissue sarcoma of the extremities. We demonstrate that a TO is significantly associated with overall survival in patients with STS-E, even when controlling for potentially confounding variables. We present here the patient and tumor characteristics that are associated with a TO in the hopes that recognition of these factors will lead to an elevation in the quality of care for these patients.

Figure 1. Kaplan Meier survival curve analysis for patients with and without a textbook outcome. In a non-parametric analysis of survival of all patients, median survival was 95.5 months (95% CI: 89.3– 102.1 months). For patients who had a TO, the median survival was 124.2 months (95% CI: 115.7– 132.3 months); among patients who did not have a TO but had negative margins and no 90-day mortality, median survival was 70.6 months (95% CI: 63.6 – 79.6 months).



Poster #226 3465411

FUNCTIONAL CONSEQUENCES OF OVEREXPRESSION OF MIR-26A AND MIR-3913 IN WDLPS AND DDLPS

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Objective: Liposarcomas are heterogeneous soft tissue sarcomas of adipocytic origin. Four histological subtypes are recognized; well differentiated (WDLPS or atypical lipomatous tumors), dedifferentiated (DDLPS), myxoid/round cell and pleomorphic liposarcomas. The subtypes are different with regard to their pathogenesis, molecular alterations and clinical behavior. WDLPS and DDLPS are the most common liposarcoma subtypes and are molecularly characterized by the presence of a neo-chromosome which predominantly consists of amplified regions of the long arm chromosome 12. The amplified 12q13-15 region includes well-known oncogenes such as MDM2 and CDK4 as well as microRNAs (miRNAs). As miRNAs can be intimately involved in sarcomagenesis we investigated the expression levels and functional roles of miRNAs located in the 12q13-15 region in WDLPS and DDLPS.

Methods: RT-PCR (Applied Biosystems) was used to quantitatively measure the expression of miRNAs in normal fat (n=17), lipomas (n=14), WDLPS (n=39) and DDLPS (n=28) and relevant cell lines (WDLPS: 93T449, 94T778 and 95T100, gift of Dr. F. Pedeutour, Nice University Hospital, Nice, France; DDLPS: LPS224, LPS246 and LPS863, gift of Dr. Y. Lu, M.D. Anderson Cancer Center, Houston, Texas, USA). Transient transfections using MiRIDIAN miRNA mimics (Dharmacon) and MiRCURY LNA™ inhibitors (Qiagen/Exiqon) were used to modulate miRNA levels in WDLPS and DDLPS cell lines after which cellular proliferation, apoptosis induction and cell cycle progression were determined. Luciferase reporter assays (psiCHECK2, Promega), Western blotting and RT-PCR were used to verify mRNA targets of selected miRNA.

Results: Based on their location on the long arm of chromosome 12 and vicinity to either MDM2 or CDK4 the following miRNA were selected: miR-26a, miR-616, miR-1228, miR-1279, miR-3913 and miR-6759. MiR-26a-5p was found overexpressed in DDLPS compared to fat, lipomas and WDLPS. In addition, miR-3913-3p and miR-3913-5p were detected to be overexpressed in WDLPS and, in a more pronounced fashion, in DDLPS compared to fat and lipomas. Similarly, miR-26a-5p was found expressed both in WDLPS and DDLPS cell lines although a 13.5 fold higher expression was observed in the DDLPS cell lines compared to WDLPS. MiR-3913-3p was expressed in both WDLPS and DDLPS cell lines at approximately equal levels. In contrast to the situation in tumor samples no expression was measured in WDLPS and DDLPS cell lines of miR-3913-5p. Inhibition of miR-26a-5p and miR-3913-3p expression affected cellular proliferation of both WDLPS and DDLPS cell lines whereas miRNA mimics had no effect. Inhibition of miR-3913-3p induced apoptosis in WDLPS cell lines but not in DDLPS. In contrast, inhibition of miR-26a-5p only slightly stimulated apoptosis in DDLPS cell lines but not in WDLPS. MiR-26a-5p was shown to regulate the tumor suppressor PTEN in the context of WDLPS and DDLPS.

Conclusion: MiR-26a and miR-3913 overexpression, possibly due to their amplification on the neo-chromosome in WDLPS and DDLPS, promotes sarcoma development by stimulating cellular proliferation and - to a lesser extent - suppressing apoptosis. MiR-26a-5p was verified to target the tumor suppressor PTEN. It is concluded that in addition to the protein coding genes, present on the neo-chromosome in WDLPS and DDLPS, also non-protein coding genes, like miRNAs, may play essential roles in sarcomagenesis.

Poster #227 3465438

MISMATCH REPAIR DEFICIENCY IN BONE AND SOFT TISSUE TUMORS: IS THERE A RATIONALE FOR ROUTINE TESTING IN ADVANCED SARCOMA?

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Objective: There has been an increased demand for MMR status testing in sarcoma patients after the success of immune checkpoint inhibition (ICI) in mismatch repair (MMR) deficient tumors. However, data on MMR deficiency in bone and soft tissue tumors is sparse, rendering it unclear if routine screening should be applied. Hence, we aimed to study the frequency of MMR deficiency in bone and soft tissue tumors after we were prompted by two (potential) Lynch syndrome patients developing sarcomas.

Methods: Immunohistochemical expression of MLH1, PMS2, MSH2 and MSH6 was assessed on tissue micro arrays (TMAs), and included chondrosarcoma (n=206), osteosarcoma (n=65), osteochondroma (n=9), enchondroma (n=11) and a mix of different soft tissue tumors (leiomyosarcoma (n=87), myxofibrosarcoma (n=17), (pleomorphic) liposarcoma (n=5), rhabdomyosarcoma (n=2), undifferentiated spindle cell sarcoma (n=9), undifferentiated pleomorphic sarcoma (n=22), radiation associated sarcoma (n=4), Ewing sarcoma (n=1), MPNST (n=1) and angiosarcoma (n=1)). If expression was heterogenous or absent, staining on whole sections followed. Molecular data was retrieved from reports, if not available MSI analysis followed and in MLH1 negative cases additional *MLH1* promoter hypermethylation analysis was performed. Furthermore, a systematic literature review on MMR deficiency in bone and soft tissue tumors was conducted.

Results: The first index case presented with a pleomorphic rhabdomyosarcoma and subsequently developed a pancreatic adenocarcinoma and an urothelial carcinoma of the ureter. The second index patient presented with a leiomyosarcoma, where after he developed acute myeloid leukaemia, a sebaceous gland carcinoma and adenocarcinoma of the coecum. Both rhabdomyosarcoma and leiomyosarcoma showed loss of expression of MSH2 and MSH6, while MLH1 and PMS2 were retained. In one patient a germline mutation in *MSH2* (p.Cys697Tyr) was present, while in the other patient the tumor showed a MSI-high phenotype. In addition, five other MMR deficient tumors were identified (5/406), which included four leiomyosarcomas and one radiation associated sarcoma. MMR deficiency in osteosarcomas and chondrosarcomas was non-existent. Molecular analysis on tumor material showed in one tumor a *MLH1* mutation (p.Val7Argfs*18), one tumor was MSI-low and one was microsatellite stable. Literature review revealed 27 MMR deficient sarcomas, of which 33% were undifferentiated/unclassifiable sarcomas. 56% of the patients had Lynch syndrome or constitutional mismatch repair deficiency syndrome.

Conclusion: MMR deficiency is extremely rare in bone and soft tissue tumors, making reflex testing for MMR deficiency in all advanced sarcoma patients debatable. Screening focusing on tumors with myogenic differentiation, undifferentiated/unclassifiable sarcomas and in patients with a genetic predisposition/co-occurrence of other malignancies can be helpful in identifying patients potentially eligible for ICI.

Poster #228 3465449

PROGNOSTIC VALUE OF PGP AS STRATIFICATION FACTOR FOR THE TREATMENT OF PATIENTS WITH NON-METASTATIC EXTREMITY HIGH-GRADE OSTEOSARCOMA: A SPANISH SOCIETY OF PEDIATRIC HEMATOLOGY AND ONCOLOGY (SEHOP) AND SPANISH GROUP FOR RESEARCH IN SARCOMAS (GEIS) STUDY

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Objective: The overexpression of *ABCB1*/P-glycoprotein (Pgp) efflux pump is a predictor of poor outcome in retrospective series of osteosarcoma. Therefore, Pgp expression was used as a stratification factor in two prospective studies in Spain and Italy.

Methods: This observational prospective study performed by the Spanish Sarcoma Group (GEIS) (NCT04383288) enrolled patients ≤ 30 years with extremity high-grade osteosarcoma. Pgp expression was centrally analyzed. Preoperatively, all patients received MAP (methotrexate, adriamycin, platinum). In case of Pgp overexpression (Pgp+), mifamurtide (2 mg/m^2 twice/week for 3 months then weekly for 6 months) was added in the adjuvant setting, with 4 consecutive cycles of ifosfamide 3 g/m^2/day, day 1-5 (HDIFO) in case of poor response (PR) to MAP. Patients without overexpression of Pgp (Pgp-) received MAP postoperatively, regardless of pathological response. From March 2013, an amendment increased high dose methotrexate (HDMTX) cumulative dose from 60 g/m^2 (5 cycles) to 120 mg/m^2 (10 cycles). At the same time, a prospective clinical trial enrolled patients with the same regimens in Italy. From 122 patients enrolled in Spain, data of patients with an adequate follow-up are presented here.

Results: From December 2013 to April 2018, 69 patients were enrolled and analyzed for Pgp expression: 40 were Pgp+, 20 were Pgp-, while the expression of Pgp was not evaluable in 9 patients. Median age was 14 years (4-32) and 57% of the patients were male. With a median follow-up of 38 months (range 11.67-69.97), the 3-year EFS and OS were 81.9% (95% CI 70.2-89.3) and 85.2% (95% CI 72-92.5), respectively. In our series, Pgp overexpression was not significantly associated with worse survival, something that could be in relation to MEPACT administration. Of note, a trend was observed between positive expression of Pgp and better 3-year EFS rate in the poor responders' population [90.5% (95% CI 67-97.5) vs 65.6% (95% CI 32-85.6), p=0.077].

Conclusion: In our study, EFS favorably compares with other previous series of high-grade osteosarcoma of extremities. The deleterious impact of Pgp could have been ameliorated by the strategy of using MEPACT in these patients. The study is still ongoing and future analyses are planned with a longer follow-up and joining both, Italian and Spanish series.

Poster #229 3465504

LATE CENTRAL NERVOUS SYSTEM AND LUNG RECURRENCE OF EWING'S SARCOMA: A CASE REPORT

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Objective: The prognosis of Ewing's sarcoma has substantially improved with early integration of modern systemic cytotoxic therapy. However, further progress is needed, as around 30% of patients with localized disease will eventually develop local or metastatic relapse. This is most often an early event, with median time to recurrence of 22 months, but late relapses have been described. Most common sites of metastasis are the lungs and bones, whereas hematogeneous spread to the nervous system (CNS) is rare, with an incidence of approximately 2%. Here, we describe a case of very late CNS and lung recurrence of Ewing's sarcoma.

Methods: A 34-year old male with a history of Ewing's sarcoma of the fibula treated 20 years before with VDC-IE and surgery presented to clinic with severe headache for 10 days, with no associated neurologic symptoms. Cranial MRI was remarkable for an intraparenchymal tumor located at the right frontal lobe, measuring 6.2 x 4.3 cm, with hetereogeneous enhancement and extensive areas of necrosis, along with an extra-axial mass in the right temporal fossa, with signs of perineural dissemination, measuring 3.2 x 1.3 cm. The patient then underwent surgical resection of the right frontal lobe lesion, and had an uneventful postoperative course.

Results: Pathologic analysis demonstrated a malignant neoplasm of small, round, blue cells with areas of hemorrhage and necrosis. On immunohistochemistry, malignant cells were positive for CD99 and FLI1. Additionally, FISH was positive for EWSR1 rearrangement, compatible with a diagnosis of Ewing's sarcoma. PET-CT was performed for staging, and demonstrated the presence of an FDG-avid left lower lobe pulmonary nodule (SUV = 11.8), measuring 4.2 x 1.8 cm; biopsy confirmed Ewing's sarcoma involving the lung. Systemic therapy was then started with ifosfamide and etoposide, and tumor was sent for comprehensive molecular profiling. Therapy has been well tolerated thus far.

Conclusion: Our case highlights the possibility of very late (20 years) metastatic recurrence of Ewing's sarcoma. Recurrent disease must always be considered as a differential diagnosis in patients with unexplained symptoms, regardless of the disease-free interval. Further analysis of risk factors for late relapses and for CNS dissemination are needed to guide optimal surveillance protocols.

Poster #230 3465518

LYMPHOVASCULAR INVASION AND HISTOPATHOLOGIC PROFILE PORTENDS WORSE PROGNOSIS IN CHONDROSARCOMA

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Objective: Despite being the second most common primary bone cancer, chondrosarcoma remains a diagnostic and treatment challenge. To date, prognostic factors such as age, grade, location, margin status and tumor size have been associated with survival. However, the histopathologic features that are most associated with survival have not been well established. The goal of this study was to identify histopathologic features of chondrosarcoma that are most associated with survival and to compare these to traditional patient, tumor and treatment variables.

Methods: We retrospectively reviewed all patients undergoing surgical resection of a primary chondrosarcoma at a single tertiary care referral center from 2006-2018. Patients were included if they had at least 2 years of follow up available. Patients were excluded with insufficient follow up, secondary malignancies and incomplete treatment details. We performed Kaplan Meier analyses to identify the factors associated with overall survival and disease free survival in univariate measures. A Cox Proportional Hazards analysis was then used to identify factors independently associated with overall 5-year survival (OS) and 5-year disease free survival (DFS).

Results: 81 patients with an average follow up of 52.9 months were eligible for inclusion. 25 tumors (30.9%) were low grade, 36 tumors (44.4%) were intermediate grade and 20 tumors (24.7%) were high grade. 18 patients (22.2%) had a local recurrence; 25 patients (30.9%) developed metastatic disease. The 5-year OS for the cohort as a whole was 69.6%, while the 5-year DFS for the cohort as a whole was 40.7%. When considering patient characteristics, age younger than the median (50 years) was associated with improved DFS (64.4% vs. 45.9% respectively, p=0.02); younger age trended towards improved OS (82.9% vs. 63.4%, p=0.08). Tumor location, race and gender were not associated with OS or DFS. When considering tumor and treatment characteristics, tumor size >8 cm was associated with worse DFS (39.3% vs. 68.5%, p=0.01) and trended towards worse OS (64.7% vs. 78.9%, p=0.12). Positive margin status was associated with worse OS (p=0.014), but, interestingly, was not associated with DFS. Chemotherapy was only given in the setting of existing metastatic disease; however, it was not independently associated with OS . While metastatic disease was associated with worse OS (p=0.0003), local recurrence was not. (p=0.68). Radiation therapy was not associated with OS or DSF. When considering histopathologic factors, increased cellularity, increased atypia, higher mitotic rate, lymphovascular invasion and dedifferentiation were all associated with worse OS and DFS (p</=0.02). Chondrosarcoma with a myxoid component was not associated with improved or worse OS or DFS. In a MV analysis investigating the independent association of pathologic factors with OS and DFS, lymphovascular invasion was associated with worse OS and DFS (HR 6.6, p=0.044 and HR 6.5, p=0.041 respectively), even when controlling for tumor grade.

Conclusion: Predicting the clinical course for chondrosarcoma remains a challenge; there is a need for better predictive tools to help inform physicians and counsel patients with regard to prognosis. This study identified an array of pathologic factors used to assess grade that are associated with survival; independent of grade, lymphovascular invasion in particular is independently associated with OS and DFS and should be considered in the pathologic evaluation of these patients.

Poster #231 3465549

IMPACT OF PATHOLOGICAL STRATIFICATION OF ADVANCED WELL DIFFERENTIATED/DEDIFFERENTIATED (WD/DD) LIPOSARCOMA (LPS) ON THE RESPONSE TO TRABECTEDIN (T)

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Objective: We showed that the FNCLCC grading system can predict the outcome of retroperitoneal WD/DD LPS. In this study, we aim at exploring the impact of the pathological stratification according to the FNCLCC grading system on response rate (RR) and progression free survival (PFS) to T in advanced/metastatic WD/DD LPS.

Methods: A retrospective analysis of all consecutive patients (pts) with advanced WD/DD LPS receiving T at our Institution from April 2003 is reported. Tumors were categorized according to the 2020 WHO classification, complemented by Evans refinement. The "cellular subvariant" (CS) was diagnosed in the presence of a non-lipogenic area with a mitotic count < 5/10HPF. Tumors with a mitotic count ≥5/10 HPF were classified as DDLPS and graded as G1 or G2 according to the FNCLCC grading system. Pts were divided into two groups: WD/CS LPS vs G2/G3 DDLPS. Logistic regression analysis was used to evaluate if FNCLCC grade and other clinic-pathological characteristics were predictors of response to T. The Kaplan-Meier method and Cox proportional-hazards model were used for survival analyses. The Response Evaluation Criteria in Solid Tumors (RECIST) was used to assess response. Any radiological reduction in the sum of the longest diameters of target lesions that did not reach the criteria for an objective partial response (PR) was defined as a minor response (MR).

Results: A total of 49 pts were included: 17 (35%) had a WDLPS/CS and 32 (65%) had a G2/G3 DDPLS. In the WDLPS/CS cohort, 10 pts had a WDLPS and 7 had a CSLPS, while in the G2/G3 DDPLS cohort, 23 pts had a G2 DDLPS and 9 had a G3 DDLPS. Among pts with WDLPS/CS, we observed 6 PR, 2 MR, 8 SD and 1 PD, for a RR of 41,1%, while pts with G2/G3 DDLPS experienced 3 PR, 13 SD and 16 PD, for a RR of 9,4%. At logistic regression analysis, WDLPS/CS was a positive predictor of response to T both at univariate analysis (OR, 8.59; 95% CI, 1.87-39.41; p = 0.006) and at multivariable analysis (OR 8.43; 95% CI, 1.69-42.12; p = 0.009). With a median follow-up time of 36.3 months, median PFS was 13.68 months for patients with WDLPS/CS and 3.24 months for patients with G2/G3 DDLPS (p = 0.0048). In the multivariable model including characteristics associated with PFS in the univariate analysis (i.e. ECOG PS), FNCLCC grade was confirmed as an independent predictor of a better PFS (HR 0.45; 95% CI, 0.22-0.94; p = 0.034). In addition, in the subgroup of pts with WDLPS/CS LPS, the presence of a myxoid-like component was associated with a trend towards longer PFS compared to pts with non-myxoid tumors (mPFS 19.5 vs 12.5 months; p = 0.059). Finally, 27 of 49 pts were previously treated with anthacyclines in our Institutuon, with a mPFS of 3 months, with no statistically significant differences among groups (2.83 months in G2/G3 DDLPS and 3.95 in WDLPS/CS LPS, p=0.49).

Conclusion: In this series RR and PFS to T were higher in pts with WDLPS/CS and, among these, in there is a slight benefit for patients with a myxoid-like component. These patients did not show a better PFS when treated with anthracyclines, suggesting that our results could not be merely explained by a more indolent disease course of WDLPS/CS LPS. These observations need to be validated in larger studies; however, if confirmed, pathological stratification could represent a new tool to predict response to T in WD/DD LPS.

Poster #232 3465550

COMPREHENSIVE IMMUNOPHENOTYPING OF SOFT TISSUE SARCOMA PATIENTS DEFINES ASSOCIATION WITH FUNCTIONALLY DISTINCT LYMPHOCYTE SUBSETS AND MAJOR SUPPRESSOR CELLS

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Objective: Soft Tissue Sarcoma (STS) have often been the subject of research as a result of advanced disease at diagnosis and therefore its poor prognosis. Clinical trials have incorporated various disease subtypes, despite its heterogeneity. Immunophenotyping could help to define a better approach for STS therapy.

Methods: This was a prospective, observational, unicentric study to evaluate the immune status of adult STS patients with advanced disease, approved by the Ethical Committee of the Faculty of Medicine of the University of Coimbra and the Coimbra Hospital and Universitary Centre (CHUC-021-19).
The study groups consisted of 26 STS patients and 37 age-matched control samples. Within STS patients, average of 50 (19-78) years old, 42% females. For control group, average of 49 (19-79) years old, 59% females.
According to histological subtypes were adipocytic tumours (n=4), skeletal-muscle tumours (n=1), smooth-muscle tumours (n=6), tumours of uncertain differentiation (n=7), undifferentiated/unclassified sarcomas (n=3), vascular tumors (n=1) and unknow classification (n=4). Patients were treated with doxorubicin, dacarbazine, ifosfamide, vincristine, docetaxel, gemcitabine, etoposide and/or trabectedin.
Extended immunological profile was performed by multi-parametric flow cytometry analysis.

Results: In STS patients compared to control group, we found a significant lymphopenia and granulocytosis. T cells showed significant alterations with decreased helper T cells and increased cytotoxic T cells, although both populations in activated (HLA-DR+) states. Central memory (CCR7+CD45RA+) and effector-memory (CCR7+CD45RA-) CD4 T cells were found increased, whereas *naïve* (CCR7-CD45RA+) were decreased in STS patients. Th1 (CD4+CXCR3+CCR6-) and Th17 (CD4+CXCR3-CCR6+), as well as Tc1 (CD8+CXCR3+CCR6-) were found increased in STS patients, with significant activation of Th1 and Tc1.
B cells were significantly decreased in STS patients. Pre-switch (CD19+CD27+IgD+) and switch memory (CD19+CD27+IgD-) B cells were found decreased with a significant increase of plasmablasts (CD19+CD27+IgD-CD38hiCD24-). STS patients were significantly deficient in cytotoxic natural killer (NK) cells (CD56dim).
Dendritic cells (DCs) were significantly decreased in STS, with major contributions of type II myeloid DCs (mDC2) and plasmacytoid DCs (pDC).
Immunosuppressive cells (regulatory T cells/Tregs and myeloid-derived suppressor cells/MDSCs) were found altered in STS. Tregs, activated (HLA-DR+) Tregs and memory (CD45RO+) Tregs were significantly increased in STS patients. Monocytic MDSCs (M-MDSCs) were also significantly increased.

Conclusion: Peripheral mononuclear cell analysis of STS patients revealed significant lymphopenia, although activated subsets (CD4 and CD8 T cells) were observed. Also, B and cytotoxic NK cells (CD56dim) were diminished, suggesting a general impaired immune cellular response in STS patients. Immune suppressive cells, Tregs and MDSC (M-MDSCs specifically), were found increased, meaning a pro-tumor contribution of the patient immune system. Immunophenotyping in STS could help to select the best individual therapeutic approach, ultimately increasing progression free survival.

Poster #233 3465551

ADVANCED DERMATOFIBROSARCOMA PROTUBERANS: EXPERIENCE FROM A SARCOMA CLINIC IN INDIA

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Objective: Dermatofibrosarcoma Protuberans (DFSP) is an exceedingly rare tumor, accounting for less than two percent of all soft-tissue sarcomas. We undertook this study to analyze the clinicopathological data of locally advanced or metastatic DFSP patients registered in our clinic over the last four years.

Methods: We retrospectively reviewed cases of advanced or metastatic DFSP, diagnosed based on expert histopathology alone, who had presented to our sarcoma medical oncology clinic between January 2016 and January 2020. Molecular confirmation of the diagnosis was done as it is not available in India.

Results: We identified a total of 14 patients who fit the inclusion criteria, with a median age of 39 years (range: 19 to 60 years). Most of the patients were males (78.6%, M:F = 11:3). Ten of the 14 cases had sarcomatous transformation as well (71.4%). The most common primary site was the trunk (11/14, 78.6%). 11 of 14 cases (78.6%) had metastatic disease and the remaining three were locally advanced and non-resectable. The most common site of metastases was the lung, with lung metastases seen in all the metastatic cases, and the median number of metastatic sites was two (range: one to five). The median time from baseline diagnosis to the development of metastases was 42 months (range: 17 to 204 months). Our patients had undergone a median of three surgeries before being registered at our center (range: one to eight) and three of the four unresectable cases who had received neoadjuvant Imatinib were subsequently able to undergo surgery. Five patients (35.7%) had received radiotherapy before registration at our clinic. The initial partial response rate to first-line Imatinib was 76.9% and the median progression-free survival (PFS) was 11 months (range: 1-50 months) after a median follow-up duration of 15 months (range: 1 to 59 months). Of the seven cases who had progressive disease on Imatinib, one was not fit for further therapy and three progressed within one month of second-line therapy: one each on dacarbazine, pazopanib, and doxorubicin. One patient who received Pazopanib in the second-line continues to have stable disease after 30 months of Pazopanib therapy. One patient had two pulmonary metastases, underwent metastatectomy, and remains disease-free eight months after metastatectomy without Imatinib therapy.

Conclusion: The necessity of combined tumor boards for (including medical, surgical, and radiation oncologists) as well as multi-modality treatment for the management of DFSPs is clearly illustrated in our study. Although molecular confirmation of the diagnosis of DFSP may be ideal, it is not necessary, considering the good responses seen with Imatinib based solely on expert histopathology review. We had a surprisingly high proportion of patients with sarcomatous transformation in our series, in contrast to their relative rarity in the West. Imatinib remains unchallenged as the first-line therapy in advanced DFSP and neoadjuvant therapy with Imatinib is a useful strategy in locally advanced, unresectable disease. The need for better options for second-line therapy is also evident, as can be inferred from the dismal outcomes with post-Imatinib therapies.

Table 1. Clinical Details of Patients with DFSP

Patient	Age (years)	Gender	Variant	Primary Site	Stage	Therapies post-Imatinib
1	33	Male	DFSP	Forehead	Locally advanced	-
2	54	Male	DFSP with FS transformation	Shoulder	Metastatic	Pazopanib, Dacarbazine
3	48	Male	DFSP with FS transformation	Trunk	Metastatic	Doxorubicin
4	35	Male	DFSP with FS transformation	Trunk	Metastatic	Doxorubicin, Dacarbazaine, Pazopanib
5	36	Male	DFSP with FS transformation	Trunk	Metastatic	-
6	19	Male	DFSP with FS transformation	Trunk	Metastatic	Pazopanib
7	35	Female	DFSP with FS transformation	Nape of neck	Metastatic	Dacarbazine
8	30	Female	DFSP	Trunk	Locally advanced	-
9	35	Male	DFSP	Trunk	Locally advanced	-
10	42	Female	DFSP with FS transformation	Trunk	Metastatic	-
11	50	Male	DFSP with FS transformation	Trunk	Metastatic	-
12	49	Male	DFSP with FS transformation	Trunk	Metastatic	-
13	48	Male	DFSP with FS transformation	Trunk	Metastatic	-
14	60	Male	DFSP	Trunk	Metastatic	-

Abbreviations: DFSP, dermatofibrosarcoma protuberans; FS, fibroscarcomatous

Poster #234 3465565

NKT-LIKE CELLS DISPLAY ALTERED PATTERNS OF MATURATION, MIGRATION, ACTIVATION AND EXPRESSION OF IMMUNE CHECKPOINTS IN SOFT TISSUE SARCOMA

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Objective: Since the lack of information regarding the role of NKT-like cells in soft tissue sarcoma (STS), we aimed at the extensive characterization of these cells in STS patients.

Methods: The Ethical Committee of the Faculty of Medicine of the University of Coimbra and the Coimbra Hospital and University Center (CHUC-021-19) approved the present exploratory study. This preliminary data comprised 8 STS patients, with an average of 50 (range 19 – 78) years old, 50% females, and 31 healthy donors (HD) with an average 54 (range 24 – 73) years old, 55% females. The histological classification of the tumors from the STS patients enrolled in the study was adipocytic (n=2), smooth muscle (n=2), vascular (n=1), uncertain differentiation (n=2), and undifferentiated (n=1). EDTA peripheral blood collected from patients and HD was processed and prepared to analyze the NKT-like population by multiparametric flow cytometry. An extensive panel of membrane receptors expressed on NKT-like cells was evaluated, which included the molecules involved in maturation (CD11b, CD27, CD57), migration (CD62L), activation (CD16, CD69, HLA-DR), NK cell receptors (NKG2A, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80) and immune checkpoints (PD-1, CD137 and CD137L). For each NKT-like population parameter analyzed both relative frequency and density per cell were assessed.

Results: Data obtained from this research revealed a different receptor expression profile in STS patients comparatively to HD. Significant alterations were found for maturation receptors: higher density of CD27 and lower expression of CD11b. Which, according to the differentiation markers on NK cells, implies a more immature state. The density of CD62L was significantly increased, suggesting enhanced migration of these cells. Observing the activation markers, we found an increased frequency of the CD69 NKT-like cells. For the C-type lectin family of receptors (NKG2A, NKG2C and NKG2D), we observed an increased density of the inhibitor NKG2A receptor. The analysis of the Natural Cytotoxic Receptors (NCRs), involved in tumor recognition, showed significant higher frequency and density of NKp30, NKp44 and NKp46. For the co-stimulatory receptor NKp80 both frequency and density were found significantly reduced. NKT-like cells also exhibited an increased expression of PD-1 and CD137 immune checkpoints (ICPs).

Conclusion: In conclusion, NKT-like cells from STS patients displayed an immature phenotype with increased expression of receptors linked to migration, activation and tumor recognition. On the other hand, the expression of NKG2A, PD-1 and CD137 suggested a more inhibited state of these cells. NKT-like cells from STS patients were phenotypically distinct from HD, although further studies are needed to clarify the role of these cells in STS. Exploration of the potential use of these parameters to stratify patients or as biomarkers of good response to therapy remains to be addressed.

Poster #235 3465580

SOCIOECONOMIC STATUS AND CANCER-RELATED MORTALITY IN SOFT TISSUUE SARCOMA: AN ANLAYSIS OF THE SEER DATABASE

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Objective: Soft tissue sarcomas are rare but devastating cancers with five-year disease specific survival approaching 60%. Treatment factors for soft tissue sarcoma including negative resection margin and radiation therapy have demonstrated reduced local recurrence and tumor specific correlates of survival include histology, size of the tumor, and presence of metastasis. Several non-modifiable risk factors have also been identified including race, sex, marital status, county average income, and geographic location (urban vs rural). Composite socioeconomic status (SES) and its contribution to overall survival has been evaluated in both osteosarcoma and for broadly categorized bone and joint sarcoma, but has yet to be studied specifically in soft tissue sarcoma. In this study, we evaluated the effect of composite SES on overall and disease-specific mortality in soft tissue sarcoma using a cancer registry.

Methods: We queried the SEER database for all soft-tissue sarcoma cases from 1975 to 2016. With data from the American Community Survey 2013-2017, we created quartiles three key measures: percentage of persons age 25 and older without a high school degree, percentage living below the poverty line, and median family income. A composite score (range 3-12) was created and initially categorized into tertiles, but following Kaplan-Meier analysis, the upper two tertiles were found to have similar survival and combined into one category. The final overall socioeconomic score was dichotomized as low (score 3 or 4) versus high (score 5 to 12). Our outcomes were cancer-related mortality and all-cause mortality, defined as time in years from diagnosis to death or last follow-up visit.

We used Kaplan-Meier survival analysis, log-rank tests, and Cox proportional hazard regression to study all-cause mortality. Cumulative incidence curves and Fine and Gray competing risks regression were used to study cancer-related mortality.

Results: In this cohort of 16,474 patients, 19% (n=3,074) were in the low SES group. Patients in the low versus high SES groups were different in terms of demographics. Those in the low SES group were more likely to be black, unmarried, uninsured, and live in a non-urban setting. There were no major differences between low vs high SES groups in tumor characteristics including primary tumor site, tumor size, and histology. However, there was a higher proportion of patients with stage IV cancer in the low SES group than in the high SES group.

Overall, there were 5,738 deaths in this cohort over nine years of follow-up for an incidence of 114 patients per 1000 person-years. Patients in the low SES group had a higher mortality rate over time. The nine-year mortality rate was 57% in the low SES group versus 50% in the high SES group (log-rank $p<0.001$). After risk adjustment, we found that patients in the low SES group had a 16% higher hazard of death (HR=1.16, 95% CI: 1.09-1.24) than those in the high SES group.

There were 4,624 cancer-related deaths in this cohort over nine years of follow-up for an incidence of 93 patients per 1000 person-years. Patients in the low SES group had a higher mortality rate over time). The nine-year mortality rate was 44% in the low SES group versus 38% in the high SES group (Gray's $p<0.001$). After risk adjustment, we found that patients in the low SES group had a 13% higher hazard of death (HR=1.13, 95% CI: 1.05-1.22) than those in the high SES group.

Conclusion: In our study of a large, nationally representative cohort of soft tissue sarcoma patients, we found that a lower composite socioeconomic status was associated with increased overall and cancer-specific mortality over nine years. This finding represents a novel contribution to the existing body of evidence on survival in patients with soft tissue sarcomas. Identifying risk factors for poor outcomes in this population, including socioeconomic status, can alert the provider to patients that may face significant constraints in their access to care and direct future research areas.

Poster #236 3465593

USE OF A HUMANIZED XENOGRAFT MURINE MODEL TO CHARACTERIZE THE TREATMENT EFFECT OF CYTOTOXIC CHEMOTHERAPY AND IMMUNOTHERAPY ON OSTEOSARCOMA

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Objective: Osteosarcoma (OS) is the most common primary malignancy of bone [1]. Unfortunately, survival outcomes have stalled, and conventional cytotoxic treatments are recognized as inadequate for a large subset of patients. Alternative approaches are needed, particularly for patients with multi-focal disease or patients who relapse. Recently, there has been growing interest in immunotherapy, [2, 3] however, early clinical results have been disappointing within the context of OS, underscoring the need for a better understanding of the immune system's role in OS development and progression. Most OS xenograft systems to date utilize patient-derived tumors and immunocompromised animals, which prevents the ability to evaluate the immune system's role in OS's development or treatment. The purpose of this proof-of-concept project was to characterize the treatment effect on OS using both conventional therapy and immunotherapy within a humanized xenograft murine model.

Methods: NOD-scid IL2rγ null (NSG) mice were commercially obtained and bred within a barrier facility. Once mice reached 4-6 weeks of age, they were administered 100cGy of radiation using a Cs source. Thereafter, they were engrafted with commercially available CD34+ stem cells that underwent expansion. Engraftment was assessed by sequential bleeding the mice from week 10 through week 16 and quantifying the population of human CD45+ cells via flow cytometry (BD LSR II). The threshold for successful humanization was defined as >25% human CD45+ cells within the peripheral blood. The OS cell line 143b was cultured, orthotopically implanted into the left tibia and allowed to grow for 5 days prior to the initiation of treatment. Twenty four mice were randomly divided into 4 equal treatment groups; Group 1 served as a control; Group 2 was treated with conventional therapy consisting of Doxorobucin and Cisplatin (Conventional Therapy); Group 3 was treated with immunotherapy consisting of Nivolumab (Immunotherapy); Group 4: was treated with combination therapy consisting of Doxorobucin, Cisplatin, and Nivolumab (Combination Therapy). Tumor growth was assessed using electronic calipers. On post-implant day 28, an amputation was performed as local control and survival was thereafter monitored. Post-mortem assessment of metastatic disease was performed. Immunohistochemistry (IHC) was performed to assess lymphocyte infiltration and PD-1/PD-L1 expression. RNA seq was performed on a select number of samples from each group.

Results: A growth difference was noted between the control group and conventional therapy group (p= 0.005) and between the control group and combination therapy group (p = 0.006). No significant difference was found between the control group and the immunotherapy group. Metastatic lung disease developed to a lesser extent in the conventional and combination therapy groups versus the control group (p=<0.05). No difference was noted between the control and immunotherapy groups. Survival was significantly different when comparing either the conventional group or the combination group to the control group (p = 0.01). IHC and RNAseq analyses are ongoing.

Conclusion: The humanized xenograft OS murine model appears to be reproducible and scalable, offering an environment which is arguably a closer representation of the human condition and may offer greater insight into the role of the immune system in OS growth and development. These results parallel early clinical experiences, in that immunotherapy does not confer added therapeutic value either alone or in combination with cytotoxic therapy. IHC and RNA seq data may offer insight into immune mediated response to OS and may provide further opportunities for investigation.

Poster #237 3465607

DEVELOPMENT OF AN UPDATED INTERNATIONAL CONSENSUS ON THE MANAGEMENT OF PRIMARY RETROPERITONEAL SARCOMA (RPS) BY TARPSWG

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Objective: The first document that articulated internationally-agreed recommendations for the optimal management of primary RPS was published by TARPSWG in 2015, and has been widely cited and utilized in multiple jurisdictions. Since then, membership in TARPSWG has expanded from 8 to 119 institutions worldwide, notable progress has been made in understanding the differing biology of histologic subtypes and the implications for patient management, and an RCT on neoadjvuvant radiotherapy has been published, necessitating a renewed consensus process to create an updated document.

Methods: Relevant evidence published and/or presented in peer-reviewed fora since 2014 was collated and presented to the membership of TARPSWG at two biannual meetings in 2019. Previous statements were reviewed and updated accordingly, as were levels of evidence and strength of recommendation. A revised document was circulated individually to members of the writing committee, and iteratively revised until consensus was achieved.

Results: Tenets of optimal management of RPS were considered under the categories of Systems of Care, Staging and Pre-Operative Assessment, Primary Surgical Approach, Adjuvant/Neoadjuvant Therapies, and Follow-up Evaluation. Of the 26 previous statements, 5 underwent major revision and 11 minor revision. 3 new statements were added. The evidence supporting management at a reference centre of expertise with a minimum annual volume of operative cases, and for review at a multidisciplinary sarcoma-specific tumour board prior to any management decision, was upgraded. The opportunity to improve outcomes through optimal initial management is highlighted. Statements were added regarding the need to tailor operative approach and administration of neo/adjuvant therapies to histologic subtype and grade. Guidance on application of the level I evidence recently generated through the randomized control trial (RCT) of preoperative radiotherapy versus surgery alone (STRASS) was added. The importance of entering patients onto the international prospective database RESAR is emphasized, as is participation in ongoing/future collaborative RCTs such as STRASS2, which compares preoperative chemotherapy to surgery alone for high risk Liposarcoma and Leiomyosarcoma of the retroperitoneum.

Conclusion: Despite expansion to more than 100 participating institutions over the past 5 years, members of TARSPSWG were able to reach consensus regarding all aspects of primary RPS management. International collaboration has expanded the quantity and quality of evidence upon which to base recommendations, and is critical to further progress through prospective data collection in registries and trials.

Poster #238 3465625

THE INTERACTION OF SKP2 WITH P27 ENHANCES IN THE PROGRESSION AND TUMOR-INITIATING PROPERTIES OF OSTEOSARCOMA

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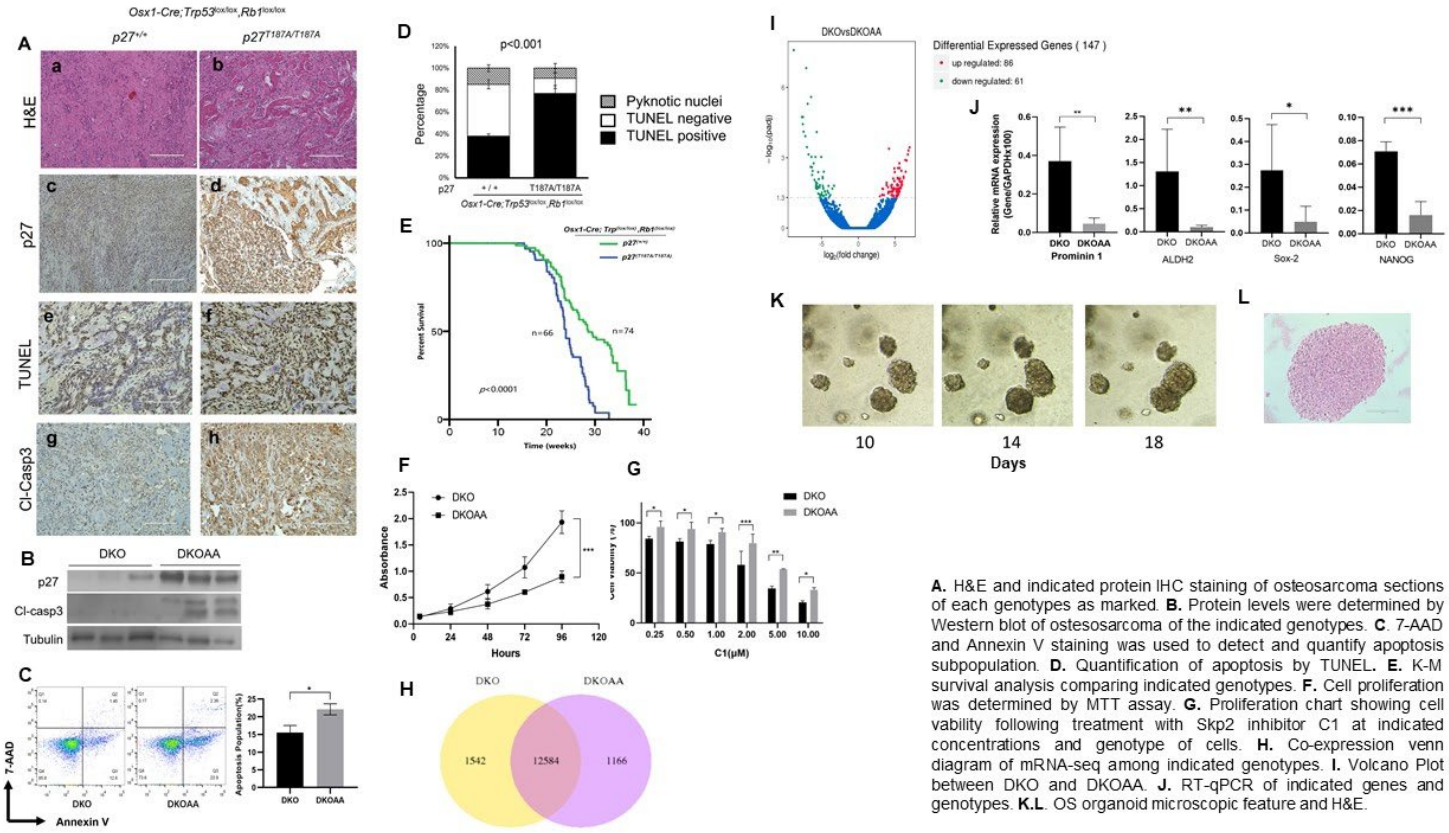
Objective: To determine the role of SCF-Skp2-mediated ubiquitination and degradation of p27 in osteosarcoma (OS) tumorigenesis.

Methods: We generated a genetically engineered mouse model (GEMM) with double knockout of Rb1 and p53 within cells of the osteoblastic lineage using the Osterix1-Cre (Osx1-Cre;$Rb1^{lox/lox}$;$Trp53^{lox/lox}$, DKO). To block the interaction between Skp2 and p27, we cross DKO mice into the p27T187A (p27:187site Thr to Ala) knock-in mutation background to create Osx1-Cre;$Rb1^{lox/lox}$;$Trp53^{lox/lox}$;$p27^{T187A/T187A}$ (DKOAA) animals. Mice of both genotypes were monitored for overall survival and tumor growth. Early passage osteosarcoma cells were harvested from mice tumors and used for further in vitro analysis. Western Blot and IHC were used for protein level determination. Annexin V staining and TUNEL assay were used for apoptosis analysis. RNA-seq and RT-qPCR were performed to compare transcriptional differences in both genotypes. A small-molecule Skp2/Cks1 pocket inhibitor (C1) was applied to DKO cell treatment. Further, mouse osteosarcoma organoids were established for validation and drug screening.

Results: All genotypes were born at the expected ratios, and mutant animals are viable, fertile, and developmentally normal. p27T187A knock-in (KI) shows an accumulation of p27 (Figure A,B) and promotes apoptosis in DKO tumors (Figure A,B,C,D). In addition, p27T187A KI significantly delayed the progression of DKO osteosarcomagenesis to lethality (Figure E). RNA-seq revealed a significant downregulation of cancer stemness markers in p27T187A compared to DKO tumors (Figure H,I,J). Finally, Skp2/Cks1 pocket inhibitor inhibits DKO instead of DKOAA OS cells, and osteosarcoma organoids were successfully established for drug tests (Figure F,G,K,L).

Conclusion: Blocking p27 degradation by Skp2 by significantly delayed osteosarcomagenesis and prolonged survival, promoted apoptosis, and reduced tumor-initiating properties in an pRb/p53 double deficient model. This study has extended our previous findings of the oncogenic role of Skp2 in OS. Further pharmacological approaches of Skp2 inhibitors may be desirable in osteosarcoma with p53 and Rb1 inactivation.



A. H&E and indicated protein IHC staining of osteosarcoma sections of each genotypes as marked. **B.** Protein levels were determined by Western blot of ostesosarcoma of the indicated genotypes. **C**. 7-AAD and Annexin V staining was used to detect and quantify apoptosis subpopulation. **D.** Quantification of apoptosis by TUNEL. **E.** K-M survival analysis comparing indicated genotypes. **F.** Cell proliferation was determined by MTT assay. **G.** Proliferation chart showing cell vability following treatment with Skp2 inhibitor C1 at indicated concentrations and genotype of cells. **H.** Co-expression venn diagram of mRNA-seq among indicated genotypes. **I.** Volcano Plot between DKO and DKOAA. **J.** RT-qPCR of indicated genes and genotypes. **K.L**. OS organoid microscopic feature and H&E.

Poster #239 3465637

LONG-TERM RESULTS OF ADJUVANT MIFAMURTIDE ALONGSIDE CHEMOTHERAPY IN THE TREATMENT OF PEDIATRIC AND ADULT PATIENTS WITH OSTEOSARCOMA

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Objective: Osteosarcoma (OS) is the most common malignant primary bone tumour. Chemotherapy (CT) is a mainstay of treatment, usually given perioperatively in localized presentations. The addition of mifamurtide (MTP), an immunomodulating agent, alongside adjuvant CT has been shown in a phase III trial to improve overall survival (OS) compared to adjuvant CT alone.

Methods: Retrospective one-centre study of patients (pts) with localized OS treated between 2009 and 2019 with perioperative CT and surgery; adjuvant CT was given alongside MPT (biweekly the 1st 12 weeks, followed by weekly for 24 weeks) for a total duration of 36 weeks. We reviewed clinical and pathological data regarding the diagnosis, treatment, pathological response to neoadjuvant CT, progression-free survival (PFS), OS and toxicity. Log-rank analysis performed for survival analysis.

Results: 22 pts; 59% male. Median age 16 years (range, 6-59). All high-grade OS; telangectasic OS in six cases. Location: Femur 11 (50%), tibia 7 (32%), humerus 3 (14%), pelvis 1 (4.5%) and mandible 1 (4.5%).
20 pts received neoadjuvant CT with doxorubicin, cisplatin and metothrexate (MTX); 2 pts proceeded directly to surgery. 3 pts older than 35 years did not receive MTX while 4 of the 10 pediatric pts (younger than 15 years) received also neoadjuvant ifosfamide.
Pathological response to CT (20 pts): 7 complete responses (35%, defined as necrosis > 95%), 8 partial responses (40%, necrosis 50-95%) and 5 poor responses (25%, necrosis < 50%).
Adjuvant CT in all patients with the same regimen as before; 10 pts received also ifosfamide (usually due to poor response). All pts but two (who progressed early) completed the whole course of adjuvant CT and MTP. No relevant grade 3-4 toxicities were seen except for a grade 3 infusional reaction.
11 pts had a relapse; pulmonary in 54%, extrapulmonary in 37% and local in 9%. Nine pts had a surgical metasectomy at some time of their evolution. Median PFS was 42 months (range 18-64 months). OS at 3 and 5 years was 77 and 70%, respectively.

In the univariate analysis for OS, patients older than 20 years fared worse than younger patients (HR 5.02, for a 95%CI of 1.19-20.83). There was a trend for worse OS in pts with no pathological complete response or with distant metastases compared to a local relapse.

Conclusion: The addition of MTP to standard CT in our patients with localized osteosarcona was feasible and well-tolerated. Our PFS and OS results are similar to those of the original Intergroup-0133 phase III trial. As has been noted in other previous studies, older patients fare worse compared to younger patients. The biological basis of this finding remains unknown.

Poster #240 3465660

ACCURACY OF X-RAY AND MAGNETIC RESONANCE IMAGING IN DEFINING THE TUMOR MARGIN IN PRIMARY BONE SARCOMA

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Objective: Primary bone sarcomas typically originate near the end of long bones and are often treated with limb-salvage surgery and endoprosthetic reconstruction. Modern technology allows physicians to use measurement software on electronic X-ray and MRI (magnetic resonance imaging) to plan the corticotomy to ensure all the intramedullary extension of the tumor will be removed and an appropriate margin is resected between the tumor and the remaining tissue. We sought to compare the margins predicted by pre-operative electronic measurements with X-ray and MRI to the final pathologic surgical margins in limb-salvage surgeries of bone tumors.

Methods: This study was a retrospective chart review of 39 patients with primary bone sarcoma treated operatively with limb-salvage surgery. The pathology reports of the resected tissue provided the length of the bony resection and the true margin from the tumor to the bone. Two non-blinded reviewers used electronic measurement tools to determine the expected margin from X-ray or MRI based on the length of tissue resected and compared with the gold standard i.e. pathology. The measurements on X-ray images used anterior-posterior and lateral films. MRI measurements were made on coronal and sagittal images. The averaged margin was calculated for X-ray by averaging the anterior-posterior and lateral margins, and for MRI by averaging the coronal and sagittal margins. We also determined the average margin error when the MRI image with the clearest tumor visualization and smallest predicted margin was used. Univariate statistical analysis was conducted on the electronic measurements to determine the variability of expected margins and overall accuracy of each imaging technique.

Results: The average absolute error of the margin measured from averaged MRI views was 0.74 cm with a standard deviation of 0.77 cm. When MRI images with the clearest tumor visualization and smallest predicted margin were selected, the average margin error and standard deviation was 0.71 cm and 0.70 cm respectively. The average absolute error of the margin measured from X-ray images was 1.11 cm with a standard deviation of 0.84 cm. There were 6 outliers of 66 MRI measurements and 14 outliers of 70 X-ray measurements as defined by an absolute error greater than 2.00 cm. MRI measurements overestimated the margin in 35/66 images and underestimated the margin in 31/66 images. X-ray measurements overestimated the margin in 30/70 images and underestimated the margin in 40/70 images.

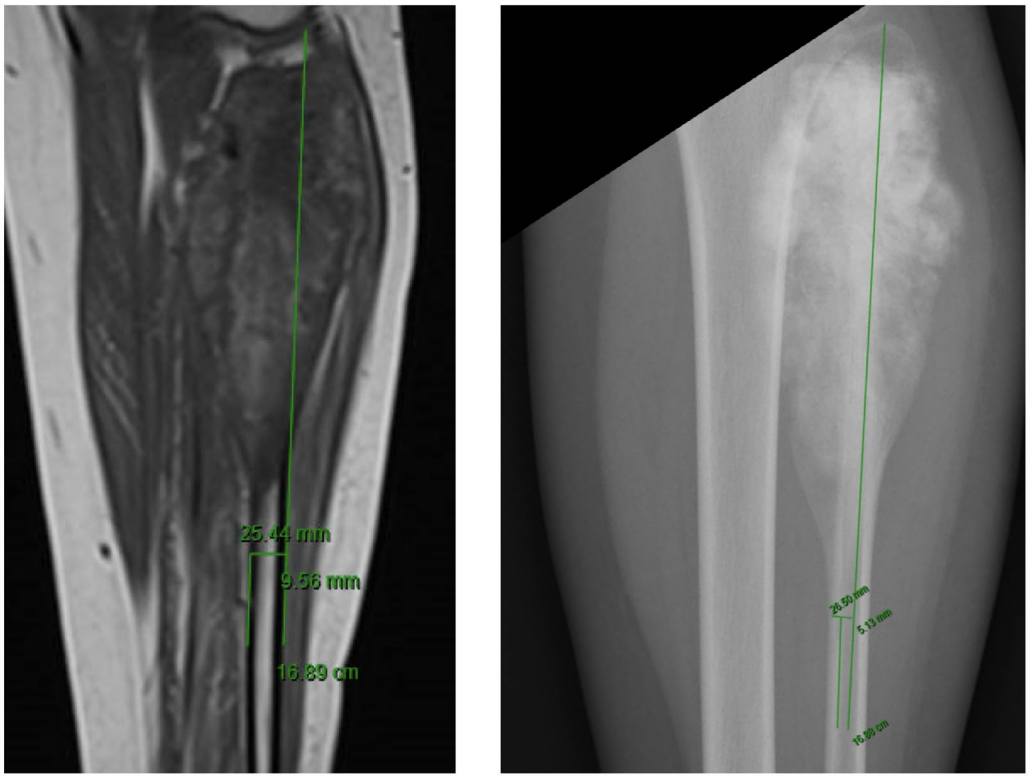
Conclusion: On average MRI provided less error in margin measurements than X-ray, in addition to lower variability. Selection of the MRI series with the clearest tumor visualization and smallest predicted margin provided the least error. Anterior-posterior X-ray measurements were more accurate than the average view measurement or the lateral view. Surgeons should measure at least 2 cm away from the edge of the tumor on MRI imaging to have an adequate margin.

Average Absolute Margin Errors of MRI and X-ray Images

Imaging	Mean (cm)	Standard Deviation (cm)
Coronal MRI	0.75	0.73
Sagittal MRI	0.83	0.76
Averaged MRI	0.74	0.77
Clear/Smallest margin MRI	0.71	0.70
Anterior-Posterior X-ray	1.09	0.79
Lateral X-ray	1.38	0.96
Averaged X-ray	1.11	0.84

The mean values and standard deviations of the absolute value of the margin error for MRI and X-ray electronic margin measurements.

Electronic margin measurements on MRI (left) and X-ray (right). The resected length was 16.9 cm and the measured margins for MRI and X-ray are 2.54 cm and 2.65 cm respectively.



Poster #241 3465668

IDENTIFICATION AND EVALUATION OF NOVEL RHABDOMYOSARCOMA ANTIGENS FOR USE IN ONCOLYTIC VACCINES

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Objective: Cancer immunotherapies focused on tumor-specific T cell response are promising therapeutic alternatives for cancer because in addition to eliminating cancer cells, they can also establish an active and long-term surveillance against relapsing tumors. The efficacy of such therapies depends primarily on the immunogenicity of the tumors. However, the lack of targetable and known specific antigens for rhabdomyosarcoma (RMS) poses as a limitation for the development of active immunotherapies against this cancer. Thus, identification of immunogenic antigens is a critical step. One such methodology for the identification of cancer antigen involves peptide elution from MHC I derived from the tissue of interest. Mass spectrometry is then performed to identify the amino acid sequence of the eluted peptides and validated for immunogenicity. The goal of this project is to identify potential RMS-associated or RMS specific antigens that can be employed in a prime-boost oncolytic vaccine.

Methods: The method for identifying RMS antigens involves first the elution of ligands from MHC I isolated from a RMS (76-9 cell line) bearing and oncolytic virus treated mouse. Mass spectrometry is then used to identify the amino acid sequence of the eluted peptides. The resulting MHC I ligands are then screened using an optimized approach involving prediction software by Dr. Shashi Gujjar (University of Dalhousie, Halifax) in order to predict the immunoprecipitates most likely to mount anti-tumor specific CD8+ T cell responses. Ligands that produce potent CD8+ T cell responses *in vitro* will then be used to immunize mice and assessed for their potential as peptide and oncolytic vaccines.

Results: The initial MHC I ligand screening from 76-9 tumor tissue and spleen led to the identification of 107 unique peptides not present in naïve spleen. Of these, up to 23 peptides were identified as having immunogenic potential based on their ability to induce cytokine production from CD8+ T cells isolated from 76-9 tumor bearing spleen.

Conclusion: Identification of peptides by way of peptide elution from MHC I and verification of their immunogenic potential through *in vitro* methods is a promising approach to discover sarcoma specific antigens. This study serves as a pipeline for the discovery of sarcoma antigens and their incorporation into T cell-based immunotherapies such as oncolytic vaccines.

Poster #242 3465674

PILOT STUDY OF THE EFFECT OF HIGH DOSES OF RADIATION ON BONE METABOLISM AND STRUCTURE IN PATIENTS TREATED WITH ADJUVANT RADIOTHERAPY AND SURGERY FOR SACRAL TUMORS.

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Objective: Despite the high rate of complications, high-dose radiation is becoming increasingly more utilized in the management of bone malignancies. In this study we investigate the impact of high dose radiation (over 70 Gy) on bone metabolism and structure.

Methods: Between September 2015 and April 2018, patients with a primary malignant bone tumor of the sacrum that were either treated with high dose radiation only or a combination of high dose radiation and surgery were prospectively enrolled at a single institution. High-dose radiation consisted of a combination of protons and photons. Dual Energy CT's (DECT's) were performed before and after radiation to determine the difference in bone mineral density (BMD) of the irradiated and non-irradiated spine. Bone histomorphometry was performed on biopsies of the irradiated sacrum and the non-irradiated iliac crest of surgical patients using a quadruple tetracycline labeling protocol. Statistical analyses were performed using the paired t-test.

Results: In total, 9 patients were enrolled; 6 with a sacral chordoma and 3 with a sacral chondrosarcoma. Two patients received radiation only and 7 patients received a combination of surgery and radiation. The average BMD of the lumbar spine did not change significantly after radiation (preradiation mean: 111.5 mg/cm3 (SD 26.3); postradiation mean: 111.3 mg/cm3 (SD 26.6); mean difference: 0.19 mg/cm3 , 95% confidence interval [CI] -3.3 – 3.6, p-value 0.90). The average BMD of the sacrum decreased significantly after radiation (preradiation mean: 122.8 mg/cm3 (SD 48.2); postradiation mean: 83.0 mg/cm3 (SD 35.7); mean difference: 39.8 mg/cm3 , 95% CI 21.7 – 57.9, p-value 0.001). The cancellous bone of the non-irradiated iliac crest had a stable bone formation rate (preradiation mean: 0.012 mm3/mm2/year (SD 0.008), postradation mean: 0.012 mm3/mm2/year (SD 0.011), mean difference -0.001 mm3/mm2/year (SD 0.004), 95% CI -0.011 – 0.008, p = 0.78), while the irradiated sacrum showed a significant decrease in bone formation rate (preradiation mean: 0.006 mm3/mm2/year (SD 0.003), postradation mean: 0.002 mm3/mm2/year (SD 0.003, mean difference 0.005 mm3/mm2/year (SD 0.003), 95% CI 0.001 – 0.008, p = 0.016.

Conclusion: This pilot study shows a decrease of bone mineral density and bone formation rate after high-dose radiation therapy. Further studies with larger cohorts and other measurements, such as serum markers of bone metabolism, are needed to get more insight into the effect of radiation on bone.

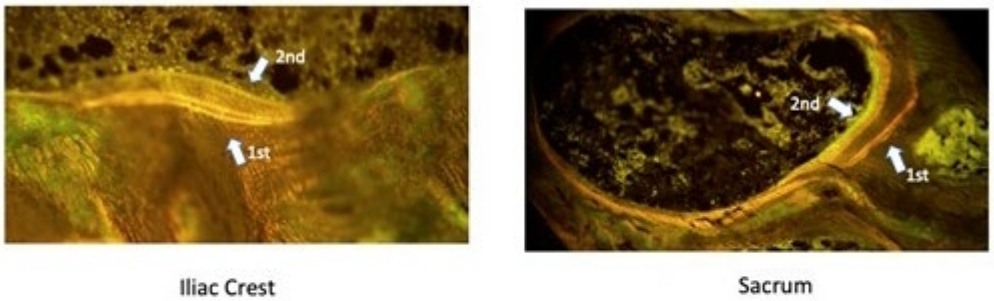

Figure 1: Representative images of cancellous bone in the iliac crest and sacrum of the same patients showing first and second set of tetracycline labels. Note the reduced extent of the second label in the sacrum following radiation treatment

Poster #243 3465693

NEURONAL INFLUENCES IN AN UNDIFFERENTIATED TUMOR: THE NERVOUS MICROENVIRONMENT OF UNDIFFERENTIATED PLEOMORPHIC SARCOMA

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Objective: Undifferentiated pleomorphic sarcoma (UPS) is a common subtype of soft tissue sarcoma, characterized by a high relapse and metastasis rate with few effective systemic therapies. Further understanding of UPS biology is urgently needed to develop novel therapies and improve clinical outcomes. Emerging evidence across various malignancies indicates that tumor innervation is associated with poor outcomes, and that nerves in the tumor microenvironment play a direct role in tumor growth, progression and metastasis, maintenance of tumor initiating cells, immune regulation, and angiogenesis, however, very little is known about the interaction between tumors and nerves in sarcomas. Our objective is to define tumor-neuronal interactions in UPS, and their influence on UPS behavior.

Methods: Histology sections from 10 human UPS samples were stained for the neuronal-specific tubulin, BIII tubulin (Tubb3), tyrosine hydroxylase (TH, sympathetic marker), choline acetyltransferase (ChAT, parasympathetic marker) and DAPI, and imaged using confocal microscopy. For mouse studies, our lab previously created a genetic mouse model of UPS containing Cre-driven oncogenic *Kras*^{G12D} and *TP53*$^{fl/fl}$, with stochastic expression of confetti fluorescent proteins that allow for *in vivo* lineage tracing or *ex vivo* cell sorting ("KPCC" mice). Bulk tumors were dissociated and two distinct subpopulations were isolated; one that does not form metastases in KPCC mice (non-metastatic, "NM") and one that reliably forms metastases in KPCC mice (metastatic, "Met"). Next, primary neuronal tissues were dissected from C57/Bl6 wild type mice; sensory neurons from dorsal root ganglia (DRG), parasympathetic neurons from embryonic submandibular glands (PSG), and sympathetic neurons from superior cervical ganglia (SCG). UPS NM and Met cells were then co-cultured with DRG, SCG, or PSG for 48 hours. UPS cell growth rate was measured using the Incucyte system (Essen Biosciences), and neurites were visualized using anti-beta-3-tubulin (Tubb3) immunofluorescence and then measured using Image J software. UPS NM and Met cells were also cultured with and without carbachol, an acetylcholine analogue, and cell confluency was measured as above.

Results: Nerves and occasional axon-like projections were observed within UPS tumors along with perineural invasion. TH and ChAT co-staining with Tubb3 suggested parasympathetic and sympathetic tumor innervation. We observed Tubb3+ cell clusters, or diffuse Tubb3 staining in UPS tumors (Figure 1). In vitro co-culture studies revealed that UPS Met and NM cells promoted neurite outgrowth in DRG and SCG compared with neurons cultured in the absence of UPS cells. DRG cultured with UPS NM cells had longer neurites compared to those cultured with UPS Met cells (142.9 um vs 107.1 um, $p<0.05$) or in the absence of UPS cells (142.9 um vs 60.2 um, $p<0.001$). UPS growth rate was not significantly impacted by co-culture with DRG, but the presence of SCG increased the growth rate of UPS Met cells by 45% at 48 hours. Addition of 50nM of carbachol to UPS NM and Met cells decreased cell growth rate by 50% at 48 hours compared to controls.

Conclusion: Nerves and axon projections are present in the microenvironment of human UPS tumors. Interestingly, tumor cells express Tubb3 in a focal or diffuse pattern. Additional studies are needed to investigate the impact of Tubb3 expression on UPS migration, invasion, and metastasis. Preliminary *in vitro* experiments suggest that UPS cells secrete factors that support neurite outgrowth. In turn, sympathetic neurotransmitters appear to enhance the proliferation rate of a metastatic UPS subpopulation, while the parasympathetic mimetic, carbachol, decreases UPS cell proliferation. Further studies are needed to define tumor-neuronal interactions in UPS *in vivo*, and in other sarcoma subtypes.

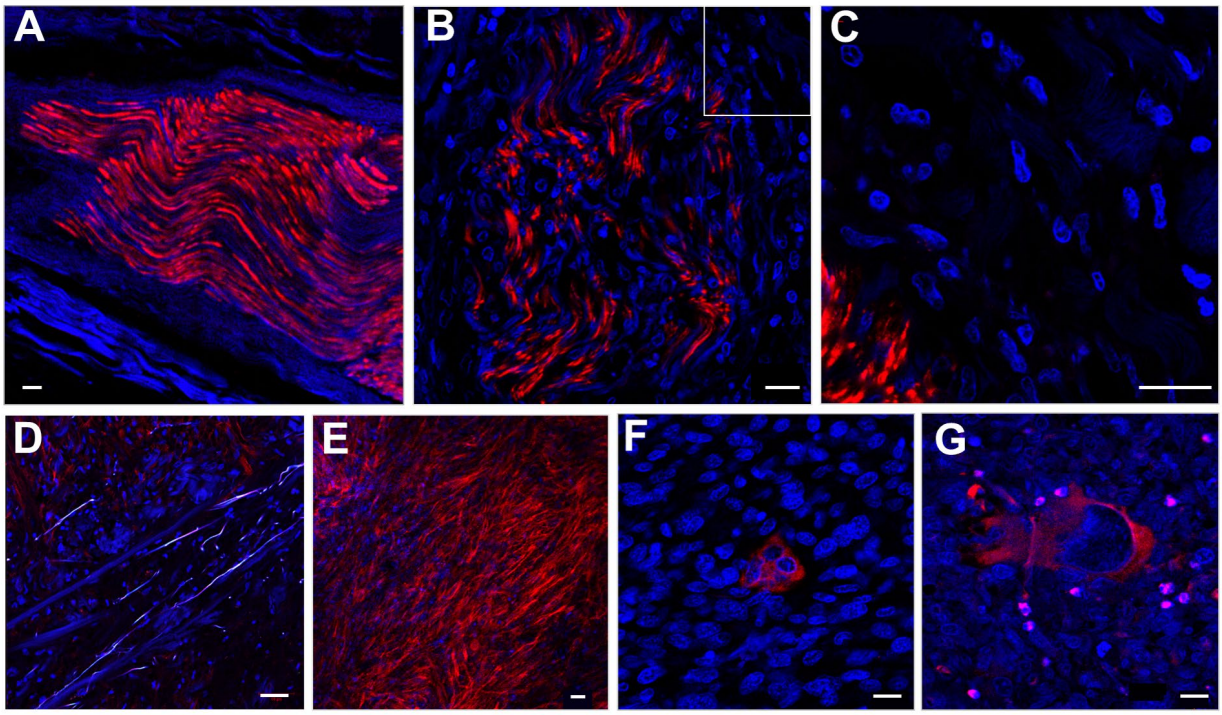

Figure 1 Tubb3 staining reveals nerves in human UPS tumors and UPS expression of neural-specific tubulin. Representative immunofluorescence confocal images of Tubb3 (red), DAPI (blue), and TH (green, D only) in human UPS tissue. (A) Nerve fascicle present in uninvolved UPS margin, scale bar = 10um. (B) Perineural invasion of tumor cells, scale bar = 20um (C) Magnified region of interest from (B), scale bar = 40um. (D) Tubb3 and TH+ axons, scale bar = 20um. (E) Diffuse Tubb3 staining in UPS, scale bar = 10um. (F,G) Tubb3+ cell cluster within UPS tumor, scale bar = 20um.

Poster #244 3465698

EVALUATION OF CANCER-TESTIS ANTIGENS IN OSTEOSRACOMA AND DEDIFFRETIATIED LIPOSARCOMA AS TARGETS FOR IMMUNOTHERAPY

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Objective: The poor prognosis of patients with advanced bone and soft-tissue sarcoma as not changed in the past several decades, highlighting the necessity for new therapeutic approaches. T-cell based immunotherapies are a promising alternative to traditional cancer treatments due to their ability to target only malignant cells, leaving benign cells unharmed. The development of successful immunotherapy requires the identification and characterization of targetable immunogenic tumor antigens. Cancer-testis antigens (CTA) are a group of highly immunogenic tumor-associated proteins that have emerged as potential targets for CD8+ T-cell recognition. Unlike other auto-antigens, CTAs exhibit restricted expression in normal tissue, limiting potential therapeutic side effects. Other parameters that are crucial for CD8+ T-cell recognition of tumor cells, such as their ability to infiltrate the tumor and the expression of HLA-peptide complexes on the surface of cancer cells, also play important roles in the outcome of immunotherapy. The goal of this study is to screen for CTA expression, HLA expression, and tumor T-cell infiltration in human dedifferentiated liposarcoma (DDLPS) and osteosarcoma (OS) by both IHC and NanoString, in order to identify targetable immunogenic antigens for T-cell based immunotherapy and to establish the immune profile of DDLPS and OS.

Methods: Human tissue micro-arrays composed of 78 cores of OS and 62 cores of DDLPS were obtained, along with matched control tissues from the same patients. IHC for the cancer testis antigens NY-ESO-1, MAGE-A3, and SSX2, was performed, and the staining results were scored by two authors based on maximal staining intensity on a scale of zero to three (absent=0, weak=1, moderate=2, or strong=3) and the percentage of tumor cells that stained. IHC for CD8 and CD3 was also performed, and T-cell tumor infiltration was defined as either brisk, nonbrisk, or absent, as described in melanoma literature. Concurrently, evaluation of 38 human DDLPS specimens and 10 healthy human fat specimens by the Nanostring nCounter platform is underway for identification of novel antigen targets and to establish the immune profile of DDLPS.

Results: Immunohistochemical analysis of CTA expression showed considerable inter- and intra-tumoral heterogeneity. DDLPS showed relatively low expression of all CTAs tested, with only 16% positive for MAGE-A3, 13% for SSX2 and 6% for NY-EOS-1. All antigens exhibited expression in low percentages of tumor cells. By contrast, in osteosarcoma, 74% of samples expressed MAGE-A3 and 68% expressed SSX, both with >80% of positive cases showing moderate to high expression. NY-ESO-1 was expressed in 41% of OS samples, predominantly at low levels. Brisk infiltration of CD8+ T cells was observed in over 70% of both sarcoma types tested. Furthermore, all sarcoma samples tested were positive for HLA expression.

Conclusion: To date, these results show promising expression of CTAs MAGE-A3 and SSX in OS, which may be used as targets in the future development of an immunotherapy for sarcoma. DDLPS shows relatively low expression, highlighting the need for more exploratory study with NanoString. The data generated throughout this project will provide insight into the immune profile of DDLPS – information that is critical for immunotherapy design.

Poster #245 3465699

EVALUATION OF BASELINE NEUTROPHIL TO LYMPHOCYTE (NLR), PLATELET TO LYMPHOCYTE (PLR) AND LYMPHOCYTE TO MONOCYTE RATIOS (LMR) AS PROGNOSTIC FACTORS IN OSTEOSARCOMA – THE TORONTO SARCOMA PROGRAM EXPERIENCE

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Objective: Across many different tumors, there is increasing evidence that systemic inflammatory response is an independent prognostic factor. Poor survival in cancer patients has been associated with high baseline values of NLR and PLR. High LMR has been associated with better outcomes. The prognostic implications of NLR, PLR and LMR are not well described in osteosarcoma. The purpose of this study is to examine the prognostic value of NLR, PLR and LMR in conventional osteosarcoma (CO), non-osteogenic bone sarcoma (NOBS) and extraskeletal osteosarcoma (ESOS).

Methods: Patients (pts) who underwent potentially curative surgery for osteosarcoma from 2000-2018 were identified from a prospectively maintained database within our program. Pts with CO, NOBS and ESOS were included. Baseline NLR, PLR and LMR were calculated from blood sample taken prior to treatment. Optimal cut-off values of NLR (3.9), PLR (222) and LMR (2.2) in predicting overall (OS) and disease-free survival (DFS) were determined based on receiver operating characteristic curve analyses. Survival were calculated using the Kaplan-Meier method.

Results: Three hundred and seventy (380) pts were identified, comprising of CO (n=240; 65%), NOBS (n=94; 25%) and ESOS (n=36; 10%). Fifty-eight percent of pts were males with median age of 40. Most pts presented with tumors affecting the limbs (79%). Forty-eight percent of pts were still alive without disease at time of evaluation, with a median follow up 183 months. In a univariate analysis, high PLR was associated with inferior OS in CO (5 yr OS 47% vs 64%, p=0.031) and in all pts (5 yr OS 46% vs 65%, p=0.039). High LMR was associated with better OS in NOBS (5 yr OS 56% vs 26%, p=0.016) and in all pts (5 yr OS 68% vs 42%, p=0.012). NLR cut off did not reach statistical significance to predict OS. Neither NLR, PLR nor LMR predict DFS, regardless of population. Analysis of pts with low NLR, low PLR and high LMR demonstrated a strong association with pts who had >90% necrotic rate (p<0.0001).

Conclusion: Our results suggest that high PLR and low LMR are associated with a worse outcome in osteosarcoma patients and is correlated with tumor necrosis rate at resection. Further work is needed to validate its use as a prognostic tool in sarcoma population.

Poster #247 3465718

IMMUNE SIGNATURE AND MOLECULAR PROFILING OF EPITHELIOID HEMANGIOENDOTHELIOMA (EHE): A TORONTO SARCOMA PROGRAM STUDY

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Objective: EHE is an exceedingly rare soft tissue sarcoma. In the metastatic setting, there is no consensus on how to best treat this disease. The spectrum of disease varies greatly between an indolent disease and aggressive disease with widespread metastases. WWTR1-CAMTA1 fusion is present in majority of cases of EHE with distant metastases, which would suggest oncogenic alterations driving a more aggressive biology. We hypothesize that a subset of EHE carry molecular aberrations that may act as strong antigenic targets for eliciting immune response.

Methods: Cases of EHE were identified from the Toronto Sarcoma Program database. Immune scoring was performed on formalin fixed paraffin embedded (FFPE) samples. The tumors were stained for tumor-infiltrating lymphocytes (TILS) i.e. CD3, CD4, CD8, CD20 and CD68. TILs were assessed using a 4-tiered scale examined under high power field (HPF) microscopy evaluation: 0 (no lymphocytes/HPF); 1 (1-10/HPF); 2 (11-50/HPF), 3 (>50/HPF). In this project we also extracted tumor DNA from FFPE samples in order to perform whole exome sequencing (WES) as well as blood samples of circulating tumor DNA estimation. Only immunoscoring results are presented within this abstract.

Results: Sixteen (16) pts have been consented to this study. Eight tissue samples have been analysed at the time of abstract submission. These were all from metastatic disease sites - liver (n= 4), lung (n= 2), soft tissue (n= 2). CD3+, CD4+, CD 8+, CD68+ T cell infiltration (threshold set >11 cells/HPF) was seen in 75%, 50%, 38% and 0% respectively in the analyzed tissue samples. All eight analyzed tissues samples showed no infiltration of CD20+.

Conclusion: Our results are showing EHE to be a "cold" tumor. This data may indicate that single agent checkpoint inhibition may be of limited value in EHE and strategies are required to turn this disease into "hot" tumors when considering immune-therapeutics. Updated data for all 16 patients will be presented at the meeting if accepted.

Poster #248 3465772

CAN INTRAOPERATIVE USE OF INDOCYANINE GREEN DYE ANGIOGRAPHY PREDICT RATES OF WOUND COMPLICATIONS IN PATIENTS UNDERGOING SOFT TISSUE RESECTION?

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Objective: Resection of extremity soft tissue sarcomas require dead space management that necessitates coverage with complex closure to local or free tissue transfer. Commonly, this tissue is compromised by neoadjuvant radiation, resulting in risk of post-operative wound complications. Indocyanine green (ICG) angiography has been used since 1966 in various specialties to assess real-time skin flap perfusion, guiding intra-operative decisions that may minimize complications in the recovery period. Little information is available in the orthopaedic surgical oncology literature on whether intraoperative SPY use can predict wound healing complications in extraskeletal soft tissue sarcoma resection. We analyzed clinical parameters and compared the utility of relative vs. absolute perfusion as measured by ICG in predicting to wound complications in patients with pre-operative radiation.

Methods: Retrospective, single institution analysis of prospectively collected data on 22 consecutive patients who underwent extremity soft tissue sarcoma resection requiring complex tissue closure with an average follow up of 12 months was performed. Tissue perfusion was assessed in the operating room (OR) pre-incision and after final skin closure. Reference areas were selected in non-dissected, reproducible areas, within the field of view of the intended incision (Figure 1). Clinical parameters including incision length, pre-operative radiation dose, serum hemoglobin post-operative day one, intraoperative use of pressors, age, smoking history, were collected via chart review. Multivariate linear regression models of clinical parameters and intra-operative SPY measurements were generated to predict to no complication, minor wound complication, and major wound complication requiring takeback to the operating room.

Results: Twenty-two patients with pre-incision and post-closure SPY scans were included in the study (Table 1). Seventy-three percent of patients received preoperative radiation with near or full dose radiation (average 49.28 Gy). Six out of sixteen patients who received preoperative radiation developed wound complications that required surgical intervention. Multivariate linear regression with variables 1) incision length, 2) hemoglobin post-operative day one, and 3) change SPY values measured 1 cm away from the incision (as referenced to the darkest portion of the frame) post closure from pre-incision predicted to wound complications with near significance (p=0.08, adjusted R2=0.61) (Table 2).

Conclusion: Indocyanine green angiography, in combination with incision length, and hemoglobin post-operative day one may be helpful in identifying skin areas at risk of developing wound complications in extremity soft tissue sarcoma patients.

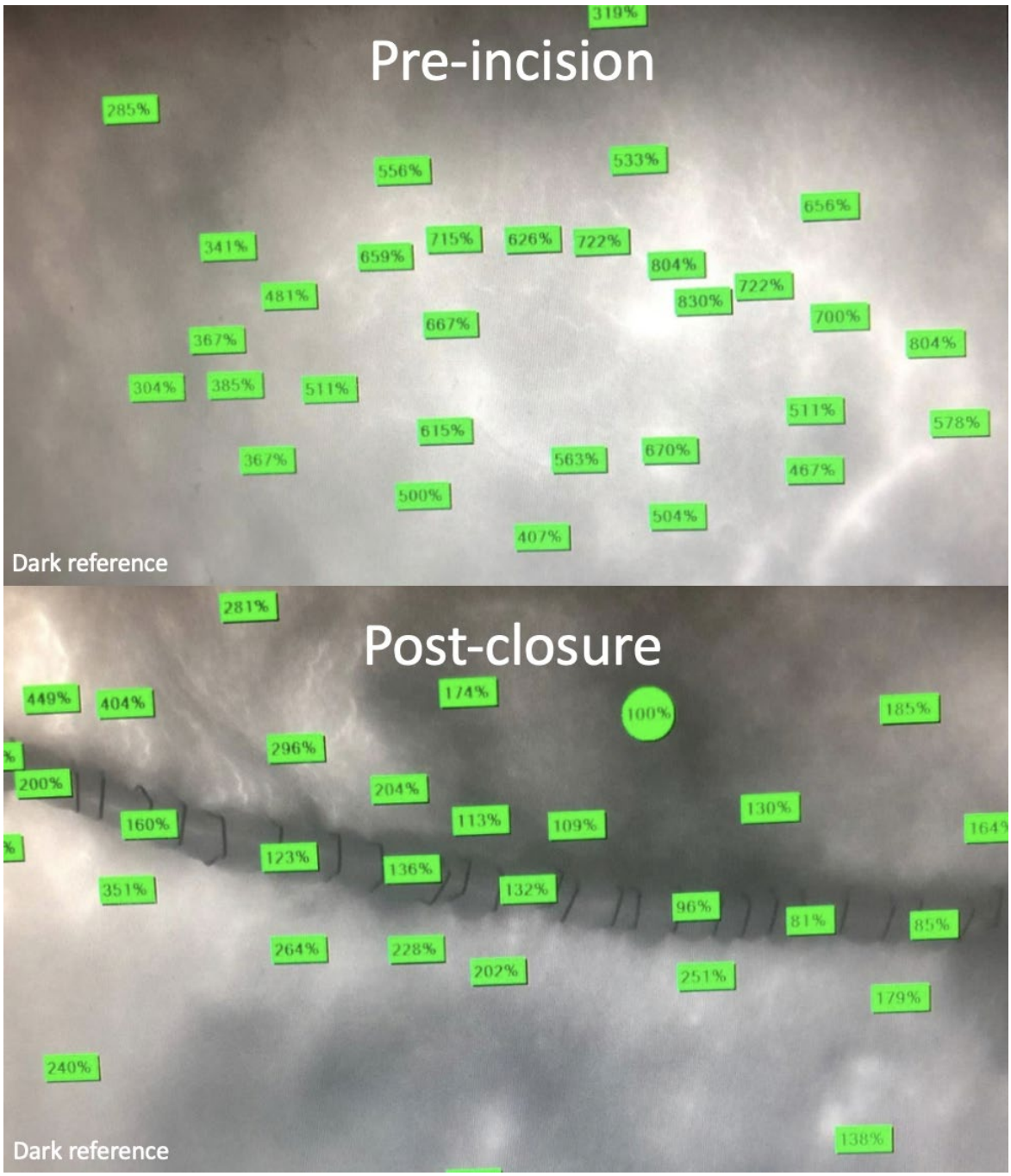
Table 1: Demographics and Characteristics

	Mean +/- SD (Range)
Average age at surgery (years)	62.91 +/- 14.17 (21-83)
Preop radiation (Gy)	48.93 +/- 2.13 (45-50)
Incision length (cm)	29.89 +/- 8.29 (10-40)
Follow up duration (years)	0.91 +/- 0.87 (0-2.84)
Hgb POD1	9.81 +/- 2.17 (6.7-13.9)

		n	%
Gender	Male	12	54.55
	Female	10	45.45
Location of incision	Forearm	1	4.55
	Lower leg	1	4.55
	Shoulder	2	9.09
	Thigh	18	81.82
	Included groin	5	22.73
Pathology	Atypical lipoma	4	18.18
	Dedifferentiated liposarcoma	2	9.09
	High-grade pleomorphic sarcoma	1	4.55
	Low grade extraskeletal myxoid chondrosarcoma	1	4.55
	Myxofibrosarcoma	2	9.09
	Myxoid liposarcoma	4	18.18
	Neuroendocrine tumor	1	4.55
	Recurrent myxoid liposarcoma	1	4.55
	Spindle cell sarcoma	2	9.09
	Undifferentiated pleomorphic sarcoma	4	18.18
Incision characteristics	Complex closure	10	45.45
	Complex closure with flap	6	27.27
	Complex closure with imbrication	4	18.18
	Deltoid flap	1	4.55
	Pedicle gracilis flap	1	4.55
	Plastics involvement	2	9.09
Complications	No complication	11	50.00
	Minor complication	4	18.18
	Major complication	7	31.82
	Patients with OR takebacks	8	36.36
Surgery Characteristics	No intraop/postop pressors	9	45.00
	1 intraop/postop pressors	11	55.00
	Blood products used	7	35.00
Patient position during case	Supine	9	45.00
	Prone	7	35.00
	Right lateral decubitus	3	15.00
	Left lateral decubitus	1	5.00
Patient characteristics	Diabetes	2	10.00
	Former smoking	8	40.00
	Current smoking	1	5.00
	Peripheral Vascular Disease	1	5.00

Predicting: Any complication (Y/N)

			Averaged Values	
			p-value	Adjusted R2
Along the incision	Dark Ref	Δ Average	0.326	
		ΔBright Ref	-	
		Δ Dark Ref	-	0.59
		Incision Length	0.273	
		Hgb POD1	0.108	
1 cm away from incision	Dark Ref	Δ Average	0.311	
		ΔBright Ref	-	
		Δ Dark Ref	-	0.61
		Incision Length	0.233	
		Hgb POD1	0.08	


Pre-incision
319%
285%
556%
533%
656%
341%
659%
715%
626%
722%
804%
722%
481%
830%
700%
667%
804%
367%
304%
385%
511%
511%
578%
615%
367%
563%
670%
467%
500%
504%
407%
Dark reference
281%
Post-closure
449%
404%
174%
100%
185%
296%
200%
204%
130%
160%
113%
109%
164%
123%
136%
351%
132%
96%
81%
85%
264%
228%
202%
251%
179%
240%
138%
Dark reference

Poster #249 3465776

20-YEAR EXPERIENCE IN THE MANAGEMENT OF PATIENTS WITH EXTRASKELETAL MYXOID CHONDROSARCOMA IN A SARCOMA REFERENCE CENTRE

Robert D. Beveridge[1], *Benjamin Domingo Arrue*[1], *Javier Perea Rojo*[1], *Ana Ferrero*[1], *Nuria Gómez Sepúlveda*[1], *Alba Torres Martinez*[1], *Carlos Puchades Olmos*[1], *Diego Soriano Polo*[1], *Guillermo Suay Montagud*[1], *Julio Linares Diaz*[1]
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Objective: Extraskeletal myxoid condrosarcoma (EMC) is a rare soft-tissue sarcoma, characterized by a specific chromosomal translocation (usually *NR4A3* rearrangements, leading to a *EWSR1-NR4A3* fusion) and an indolent but protacted course, with a tendency for late local and systemic relapses, even years after the original diagnosis.

Methods: Retrospective study of patients (pts) with EMC treated at our institution between 1999 and 2019. We reviewed clinical and pathological baseline data, treatments given, local and systemic relapse rates, time to local and distant metastases and overall survival (OS). Survival times were calculated with the Kaplan-Meier method. Univariate analysis for OS was performed with the log-rank test.

Results: 15 pts. 60% male. Median age 46 years (range 17-83 years). Location: 60% lower limbs, 27% trunk, 13% upper limbs. Deep tumours in 67% of cases; superficial location in 33%. None were metastatic at diagnosis. All had surgery as an initial treatment modality. Adjuvant radiotherapy in 27%. 6.7% received adjuvant chemotherapy (CT).
9 pts (60%) had a systemic relapse; median time to distant metastases: 24 months (range 6-144 months); in 7 pts (78%) there was a pulmonary relapse. Of these 9 pts, 6 (40%) had a local relapse, previous or synchronous; median time to local relapse was 18 months (range 7-102 months).
Treatment of local relapse was further surger in 83% or other local therapies un 17%. Treatment of distant metastases was surgery in 4 pts (45%), 1st line CT in 3 pts (34%, 2 pts with trabectedin and 1 pt with doxorubicin) and watchful waiting in 2 pts (22%). The three pts received 2nd line CT (2 doxorrubicin and 1 trabectedin). No responses were seen with doxorrubicin but two patients had a prolonged stabilization of disease with trabectedin.
With a median follow-up of 144 months (range 6-270 months), median OS is 28.5 months (range 13-58 months); six pts are free of disease, 3 pts are alive with disease and six have died of disease progression. No factors were statistically significant for OS in the univariate analysis.

Conclusion: Management of EMC remains unsatisfactory. The long-term risk of relapse is high and long-term follow-up is needed. Local relapse predicts a systemic relapse in most cases. There are hints of a higher activity of trabectedin for the treatment of advanced disease compared to other agents; the characteristic chromosomal translocations seen in most cases may justify this higher activity.

Poster #250 3465785

SAFETY OF DISCHARGE AT HIGHER SERUM METHOTREXATE LEVELS IN PEDIATRIC OSTEOSARCOMA PATIENTS

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Objective: Our goal is to study the effect of MTX level at the time of discharge on delay in treatment, acute toxicity, and end of therapy kidney function. Pediatric osteosarcoma patients are treated with high dose methotrexate, doxorubicin, and cis platinum. Acute toxicities from methotrexate may include renal and liver impairment; common toxicities include mucositis and nausea. The current recommended serum level of methotrexate for discharge is less than or equal to 0.1 mg/dL. Increasing the discharge level to less than or equal to 0.15 mg/dL allows earlier patient discharges and reduced risk of hospital acquired infections. However, the safety of this higher serum level of methotrexate is unknown. We wish to study if toxicity induced treatment delay was more common at a higher than standard discharge level, or if earlier discharge did not cause increased risk.

Methods: We performed a retrospective review of pediatric osteosarcoma patients from January 1st, 2010 through March 1st, 2020 undergoing methotrexate therapy. The primary endpoint of this review being any delay of treatment due to methotrexate toxicity. Delay in treatment is correlated with lower survival.

Results: In 271 cycles of methotrexate treatment in 30 patients, a total of 99 discharges at a level between 0.15-0.11 mg/dL were performed. Throughout these 271 cycles there were 40 delays of treatment with no correlation between "early" discharges and delays during or after treatment. There is no correlation between the number of early discharges and changes in creatinine or bilirubin when compared between early discharge and normal discharge patients, with a p value of 0.5102 and 0.5284 for creatinine and bilirubin, respectively. Our results show no significant increase in delay of treatment, creatinine, or bilirubin if discharged with a methotrexate level of 0.15-0.11 compared to less than 0.10.

Conclusion: The average time spent in the hospital to decrease serum methotrexate levels from 0.15-0.11 mg/dL to less than or equal to 0.1 mg/dL was between 8-12 hours. Our results suggest that if the serum methotrexate level for discharge was increased to less than or equal to 0.15 mg/dL, this would decrease time spent in the hospital without increasing risk of delay of treatment.

Age at Diagnosis	BSA(m2)	Average dose (g/m2)	**"Early" Discharges (0.15-0.11 mg/dL)**	Treatments	Overall ΔCreatinine	Overall ΔALT	Overall ΔBilirubin	Avg MTX at discharge	Total delays
27	1.63	10.25	**0**	4	0.04	9	0.2	0.050	1
24	1.78	11.2	**0**	12	0.22	71	0.2	0.068	1
29	1.74	11.4	**0**	6	0.16	11	0.5	0.083	1
18	1.84	10.9	**0**	4	-0.1	28	0.1	0.063	0
29	2.18	9.17	**0**	12	-0.01	40	0.2	0.066	0
15	1.55	12	**0**	12	0.00	220	0.3	0.090	1
23	2.19	9	**1**	12	-0.03	27	0.6	0.075	4
49	1.73	10.12	**1**	4	-0.01	-140	-0.3	0.100	1
14	2	10	**1**	12	0.37	238	0.2	0.134	0
22	1.74	12	**1**	8	-0.12	152	0.3	0.086	3
16	1.42	12	**1**	4	-0.06	217	0.0	0.085	0
13	1.3	12	**1**	12	-0.07	120	0.3	0.085	0
17	2.14	9.35	**1**	2	1.10	32	0.5	0.105	1
22	1.73	11.6	**1**	12	0.10	17	0.3	0.083	0
8	0.97	12	**2**	12	0.06	26	0.1	0.095	1
22	1.75	11.4	**2**	12	0.13	-15	0.1	0.095	0
7	0.98	12	**2**	8	0.12	42	0.1	0.168	1
15	1.53	12	**2**	12	-0.08	19	0.1	0.086	2
17	1.82	11	**3**	12	-0.06	51	0.0	0.108	3
31	1.9	10.53	**4**	5	-0.06	121	0.5	0.124	0
18	1.83	10.9	**4**	12	-0.06	-4	0.1	0.105	2
11	1.25	12	**4**	10	0.09	117	0.0	0.095	1
6	1	12	**7**	12	-0.11	3	0.1	0.105	4
16	2.06	9.7	**7**	12	0.14	206	0.2	0.105	2
40	2.24	6.7	**7**	8	0.35	26	-0.3	0.128	0
17	1.86	10.8	**7**	12	0.12	38	0.4	0.120	1
15	1.59	12	**7**	12	0.10	-3	0.5	0.110	0
14	1.7	12	**8**	12	0.03	60	0.1	0.116	2
12	1.93	10.4	**9**	12	0.04	-212	0.3	0.118	1
23	2.25	8.9	**9**	12	-0.12	-95	0.0	0.130	0

Poster #251 3465792

IDENTIFYING MODIFIABLE AND NON-MODIFIABLE RISK FACTORS FOR READMISSION AND SHORT TERM MORTALITY IN OSTEOSARCOMA

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[2]*Department of Surgery, Duke University Medical Center, Durham, North Carolina, UNITED STATES*

Objective: The Centers for Medicare & Medical Services (CMS) has placed increased pressure on physicians to place an emphasis on improving patient outcomes and health care efficiency. Within Orthopaedics, this has translated to increasing efforts aimed at identifying predictors of readmission with the goal of risk stratification and optimization of patient comorbidities. Such efforts in Orthopaedic oncology are lacking, presumably owing to the fact that many of the factors predictive of mortality or readmission are either non-modifiable or cannot wait to be modified as a result of their malignancy and need for treatment. Nonetheless, this area of study can help inform patient counseling and help with anticipatory guidance in the management of these challenging patients. The goal of this study was to identify modifiable and non-modifiable factors independently associated with 30-day readmission and short term (90 day) mortality for patients undergoing surgical resection of osteosarcoma.

Methods: We retrospectively reviewed all patients (n = 5293) undergoing surgical resection of primary osteosarcoma in the National Cancer Database (NCDB) from 2004 through 2015. Inclusion criteria included all patients that had data on readmission. of these patients, 4952 had data on 90-day mortality for analysis. Univariate associations of demographics and risk factors with readmission and short-term mortality were assessed with chi-squared and logistic regressions. A multivariate logistic regression was used to determine the variables independently correlated with readmission and short-term mortality while controlling for potential confounders.

Results: We found that there were 210 readmissions (3.97%), and there was no significant change in 30- day unplanned readmission rates over this time (p = 0.76). After controlling for confounders, non-modifiable risk factors independently associated with unplanned 30-day readmission included Medicare insurance status (HR 2.0, p=0.012) and axial skeleton location (HR 1.5, p=0.03). A potentially modifiable risk factor independently associated with unplanned readmission was comorbidity burden (HR 2.5, p=0.04). Surgery type and age were not associated with risk of readmission.

91 patients died within 90 days of their surgery (1.84%); there were no significant changes in short-term mortality over the study period (p=0.16). After controlling for confounders, non-modifiable risk factors independently associated with 90-day mortality included age (HR 1.1, p<0.001), higher grade (HR 1.7, p=0.007), increasing tumor size (HR 2.2, p=0.03) and metastatic disease at presentation (HR 8.5, p<0.001). Neither insurance status nor tumor location were associated with risk of short-term mortality. Potentially modifiable risk factors independently associated with short term mortality included increasing comorbidity burden (HR 6.6, p=0.001) and amputation (HR 2.0, p=0.04). Of note, chemotherapy was associated with decreased risk of short-term mortality (p<0.001).

Conclusion: After investigating unplanned postoperative readmission and short-term mortality rates, in the largest cohort of osteosarcoma patients available, we found several trends. Insurance status, tumor location and comorbidity burden were independently associated with readmission rate, and age, amputation, grade, tumor size, metastatic disease and comorbidity burden were independently associated with short term mortality. Modifiable risk factors should be considered to help optimize short term outcomes while consideration of non-modifiable risk factors should be taken when anticipating short term outcomes and counseling patients.

Poster #252 3465794

SURVIVAL OUTCOMES IN PATIENTS WITH RETROPERITONEAL SARCOMA (RPS): AN ANALYSIS OF THE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) DATABASE

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Objective: The primary treatment for RPS is surgical resection. Radiation therapy (RT) has previously been shown to improve local control but impact on overall survival (OS) remains unclear. When indicated, RT can be delivered in the neoadjuvant, intraoperative (IORT) or post-operative setting (PORT). There is limited data available comparing RT timing. The role of chemotherapy in RPS is not well defined.

Methods: The SEER 18 registries database was queried to identify patients 18 and older with pathologically confirmed soft tissue sarcoma of the retroperitoneum (C48) diagnosed from 2004-2015. Patients diagnosed prior to 2004 were not included in order to obtain a modern cohort of patients with chemotherapy data available. Patients with metastatic disease were excluded. Patients with involved lymph nodes, formerly classified as stage IV, were included as long as distant metastases were not present. The primary endpoint of this study was OS, which was determined using the Kaplan and Meier method and compared using log rank analysis.

Results: A total of 1,963 patients were identified that met inclusion criteria, including 1,054 females and 909 males. The median age at diagnosis was 61 (range 18-96). The intent of surgical resection was radical/complete in 909 patients and local/partial in 759 patients. 295 patients did not undergo surgical resection, or had an unknown surgical status. 820 patients had grade I/II tumors and 824 had grade III or undifferentiated tumors. 124 tumors were 5cm or less in size and 1,678 were >5cm. 5 year OS was 60.5% in patients that had partial excision, 59.9% in patients that had complete excision and 25.7% in patients who did not undergo surgery or had an unknown surgical status. The latter was associated with inferior OS with a HR of 2.96 (95% CI 2.35-3.73) when compared to radical/complete excision and 3.19 (95% CI 2.53-4.03) when compared to local/partial excision. 296 patients were known to receive chemotherapy and 508 RT (27 IORT, 105 neoadjuvant and 376 PORT). The use of RT and/or chemotherapy did not improve OS in all comers, patients who had incomplete resection nor patients who had complete resection. However, RT was associated with improved OS in patients with higher grade tumors with a HR of 0.72 (95% CI 0.60-0.87). The 5 year OS was 38.3% without RT and 46.9% with RT in this subgroup of patients (p=0.0008). There was no benefit seen with RT when limited to patients with large (>5cm) tumors. No differences in OS were seen according to the timing of RT.

Conclusion: Surgical excision was associated with improved OS in patients with RPS but there was no apparent difference with respect to the extent of resection. Use of chemotherapy and RT did not improve OS in all comers but those with high grade disease who received RT had superior OS compared to patients that did not. In patients that received RT, the timing did not impact OS.

Poster #253 3465805

CLINICAL OUTCOMES OF PATIENTS WITH SARCOMA HARBORING TP53 GERMINATIVE MUTATION – A SINGLE CENTER RETROSPECTIVE ANALYSIS

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Objective: We seek to characterize a cohort of patients harboring TP53 germinative mutation (Li Fraumeni syndrome) who were diagnosed with sarcoma and to describe clinical characteristics and treatment outcome.

Methods: We performed a retrospective analysis of patients with histologically confirmed soft tissue sarcoma or bone sarcoma treated in our center between January 2000 and May 2020. Clinical variables were age, gender, tumor location and histology, family history of cancer, symptoms at diagnosis, treatment patterns, site of relapse. Survival analysis were conducted by the Kaplan-Meier method and compared with log-rank test.

Results: Twenty-three patients with soft tissue and/or bone sarcoma diagnosed with Li Fraumeni syndrome were identified at our institutional database. Median age at sarcoma diagnosis was 46 years (range: 10 – 64 yo). Fourteen patients were female (61%) and 9 male (39%). Fifteen patients (65%) had a personal history of a second neoplasm. Five types of germinative mutation in *TP53* gene were identified: c.1010G>A (p.Arg337His), n=19 (82.6%); c.919+1G>A, n=1 (4.3%); c.394A>T (p.Lys132*), n=1 (4.3%); c.375G>A (p.Thr125=), n=1 (4.3%); c.1009C>T (p.Arg337Cys), n=1 (4.3%). Seven patients (30%) had the diagnosis of a TP53 germinative mutation when sarcoma was diagnosed. Leiomyosarcoma was found in eleven patients (48%), high-grade pleomorphic sarcoma in seven (30%), rhabdomyosarcoma in two (9%), chondrosarcoma in one (4.3%), osteosarcoma in one (4.3%), and a dedifferentiated liposarcoma in one (4.3%), and 14 had histologic grade determined: grade 3 (n=8; 34.8%), grade 2 (n=5; 21.7%), and grade 1 (n=1; 4.3%). Sites of primary lesion were retroperitoneum (n=10; 43.5%), lower extremity (n=7; 30.4%), head/neck (n=2; 8.7%), upper extremity (n=2; 8.7%), and breast (n=2; 8.7%). Two patients (8.7%) had metastasis at diagnosis, one to the lung and the other to soft tissue. All patients underwent surgery as first treatment, including the two metastatic patients who were also submitted to metastasectomy. Eleven patients (47.8%) received doxorubicin-based chemotherapy (CT), which was neoadjuvant in 5 patients (21.7%) and adjuvant in 6 (26.1%). Five patients (21.7%) received adjuvant radiotherapy (RT) and two patients (8.7%) neoadjuvant RT. After a median follow up of 7 years (IQR: 7 y – 21 y), median OS of the entire cohort was 33.5 years (IQR: 12.5 y – 33.5 y). No statistically difference in OS was seen between patients who received adjuvant/neoadjuvant CT and those who did not (OS=33.5y *vs* NR, p=0.95). Twelve (52%) patients relapsed after first treatment. Four patients received one or more lines of chemotherapy for metastatic disease; none of them presenting response by RECIST (maximal response was stable disease). At the end of follow up period, five patients (21.7%) had died; in three of them, death was related to metastatic cancer other than sarcoma, and in two it was sarcoma related.

Conclusion: In this single center retrospective analysis, patients with germinative TP53 mutation-associated sarcomas we found a predominance of c.1010G>A (p.Arg337His) mutation, younger age at diagnosis and relatively more retroperitoneum than extremities tumors. Our cohort presented prolonged OS, however the prognostic value of germline *TP53* mutation for patients with sarcomas needs to be better defined by larger studies. Multicenter cooperation will be needed to understand if the disease behavior might be different according to type of mutation.

Poster #254 3465814

WHY DO ORTHOPAEDIC ONCOLOGY PATIENTS UNDERGOING PROSTHETIC RECONSTRUCTION GET READMITTED?

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Objective: Orthopaedic oncology patients are particularly susceptible to increased readmission rates and poor surgical outcomes, yet little is known about readmission rates and early morbidity. Thus, there is a need for better predictors of readmission and poor short-term outcomes. The goal of this study was to identify factors independently associated with uplanned readmission within 90 days for patients undergoing oncologic resection and subsequent prosthetic reconstruction.

Methods: This was a retrospective comparative cohort study. We included all patients treated from 2013-2019 at a single tertiary care referral institution who underwent prosthetic reconstruction by an Orthopaedic Oncologist for an oncologic diagnosis. Patients considered eligible for inclusion were those who underwent a primary prosthetic reconstruction for an oncologic resection of primary or metastatic bone tumor as well as those who underwent a revision prosthetic reconstruction for tumor recurrence or prosthetic complication if the primary prosthetic reconstruction was performed for an oncologic resection. We excluded patients who underwent prophylactic fixation with internal fixation and those who underwent prosthetic reconstruction by an Orthopaedic Oncologist for a non-oncologic reason. The primary outcome measure was unplanned 90-day unplanned readmission; minimum follow-up for our cohort was set at 90 days. Univariate statistical methods were used to factors associated with readmission. A multivariate Cox regression analysis was then built to determine independent correlation with readmission.

Results: 171 patients were identified who underwent 212 surgeries. 153 surgeries were primary prosthetic reconstructions for tumor resection; 59 surgeries were revision prosthetic reconstructions for tumor recurrence or revisions for complications involving a prior oncologic prosthetic reconstruction. There were 63 readmissions overall (29.7%). There was no difference between primary and revision reconstructions in readmission rate (31.4% and 25.4%, respectively, p=0.4). Among patient characteristics and Elixhauser comorbidities, metastatic disease status and diabetes were associated with readmission (p=0.02 and 0.045, respectively). When considering tumor and treatment characteristics among all patients, only preoperative chemotherapy receipt was associated with risk of readmission (p=0.05). Age, gender, race, ASA score, and BMI were not associated with risk of readmission.

In subgroup analysis of the primary patients, private insurance status was associated with risk of readmission. Further, among patients who underwent primary reconstruction, procedure duration and surgical blood loss were associated with risk of readmission (p=0.05 and 0.036, respectively). Among patients who underwent revision reconstruction, female gender (p<0.001), metastatic disease (p=0.009), and presence of a solid tumor (p=0.05) was associated with risk of readmission. Additionally, procedure duration, hospital length of stay, and discharge to a rehab or skilled nursing facility was associated with risk of readmission (p= 0.02, 0.02, and 0.026, respectively). Interestingly, reconstruction type (endoprosthetic vs. simple arthroplasty), tumor type (primary vs. metastatic), and tumor grade were not associated with risk of readmission.

In a multivariate analysis, ASA score, private insurance status, and hospital length of stay were independently associated with risk of readmission (p</=0.02). Elixhauser comorbidities independently associated with readmission included CHF, coagulopathy, diabetes, lymphoma, and metastatic disease (p</= 0.03).

Conclusion: This study found that readmission rates for prosthetic reconstructions for orthopaedic oncologic resections are high. The factors associated with 90-day readmission appear to differ between primary and revision surgeries. While predicting readmission remains challenging, risk stratification presents a viable option for helping minimize unplanned readmissions.

Poster #255 3465821

DENOSUMAB IN THE MULTIDISCIPLINARY MANAGEMENT OF GIANT-CELL BONE TUMOURS. LONG-TERM EFFICACY AND TOXICITY DATA

Robert D. Beveridge[1], *Alba Torres Martinez*[1], *Carlos Puchades Olmos*[1], *Benjamin Domingo Arrue*[1], *Diego Soriano Polo*[1], *Guillermo Suay Montagud*[1], *Ana Ferrero*[1], *Javier Perea Rojo*[1], *Nuria Gómez Sepúlveda*[1], *Julio Linares Diaz*[1]
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Objective: Giant-cell bone tumours (GCT) are rare bone neoplasms that frequently appear in the epyphisis of young patients. Although the risk of metastases is extremely low, they are locally aggressive tumours and are usually symptomatic, with a high risk of local relapse. Treatment is still mainly surgical; however, in unresectable, not amenable to further surgery or disseminated GCT, denosumab, an antibody against the *RANK-RANKL* signaling pathway, has been approved for use. We review our data with denosumab and TCG in the last few years since widespread regulatory approval.

Methods: Retrospective study of all patients (pts) with CGT treated at our institution between 2008 and 2019 and of those pts treated with denosumab at the standard dose of 120 mg subcutaneously every 28 days (with two charging doses in the first month of treatment). All pts received supplementary calcium. We reviewed clinical and baseline data, previous locoregional treatments given, response rates to denosumab, failure patterns and toxicity.

Results: 35 pts were analyzed. 68% were female; median age was 24 years (range 20-57 years). Long bones were most commonly affected: femur (8 pts, 23%), radius (7 pts, 20%), tibia (6 pts, 17%), humerus (1 pt, 3%); there were 4 pelvic (11%) and 4 axial skeleton cases (11%).
26 pts (74%) had surgery as an initial maneuver; the remaining 9 pts (26%) were considered inoperable at diagnosis. Of those 26 pts initially resected, 8 (31%) had a local relapse, of which three of them (12%) were deemed unresectable 17 pts (49%) finally received denosumab; 12 of these pts (34%) received denosumab with an initial neoadjuvant intention in order to operate further on, while the other five pts (15%) were always considered unresectable.
Although most patients had a symptomatic improvement with the use of denosumab, standard radiological response rates showed in most cases a stabilization of disease (11 pts, 65%); the remaining 6 pts (35%) showed a radiological partial response. No progressions or distant metastases have been seen in the whole cohort.
Surgery was performed in 6 pts (35%) after neoadjuvant denosumab; all were curettage procedures and no major surgery was needed. Median time to surgery was 6 months (range 4-12 months). In 4 of these cases, a major pathological response was seen.
Denosumab treatment was well tolerated in most cases, with only an episode of grade 1 hypocalcemia and grade 2 jaw osteonecrosis. With a median follow-up of 50 months (range 12-84 months), no progressions or distant metastases have been seen in the whole cohort. No pts have discontinued treatment due to toxicity.

Conclusion: Denosumab should be used in pts with unresectable GCT or in those cases were surgery would be mutilating or offer poor functional results. In some cases, short-term neoadjuvant denosumab can avoid mayor surgery. Long-term use seems safe, with no concerning late side effects. There is a lag between the clinical improvement seen in most cases and the pathological response rates, compared to the standard radiological assessment; novel radiological evaluation criteria should be evaluated. Future studies should focus on the optimal duration of denosumab treatment.

Poster #256 3465823

SYNCHRONOUS CO-LOCALIZATION OF GIST AND PERITONEAL MESOTHELIOMA: A SINGLE INSTITUTION CASE SERIES

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Objective: Gastrointestinal stromal tumor (GIST) has been recently associated with increased risk of additional cancers (Murphy et *al. Cancer*, 2015), including peritoneal mesothelioma (PM), a rare disease with several subtypes, including malignant mesothelioma (MM) and well differentiated papillary mesothelioma (WDPM). We investigated our single institution series of surgically resected patients diagnosed with both GIST and PM.

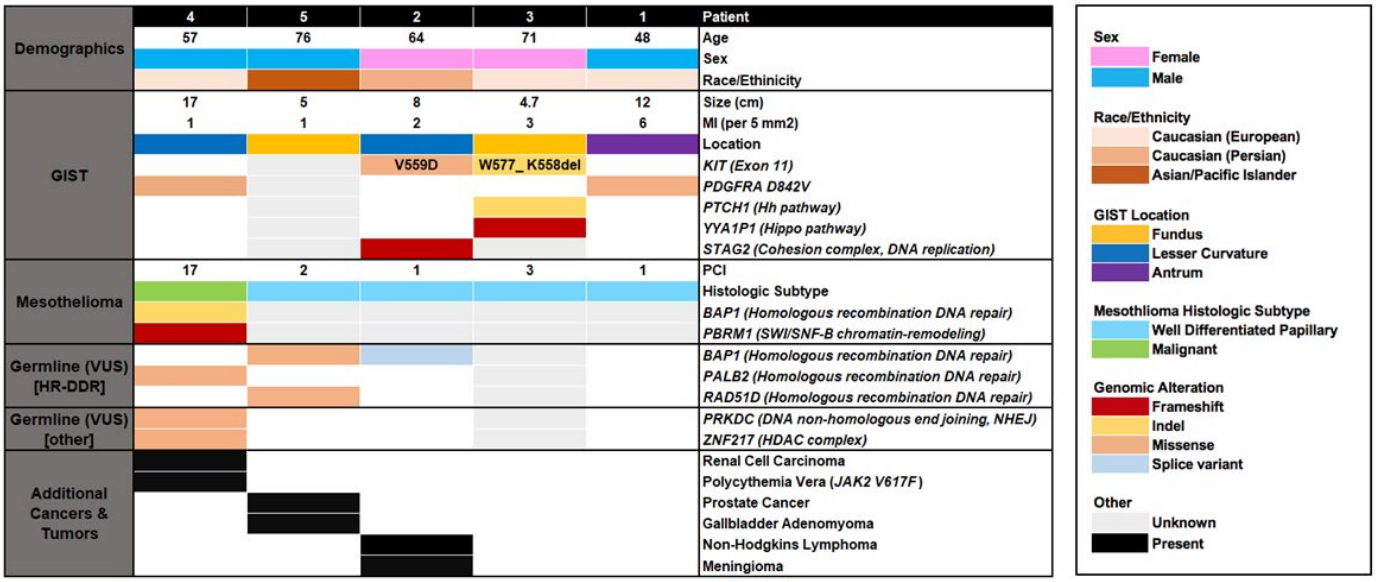
Methods: Under an IRB-approved protocol, we conducted a retrospective analysis of surgical patients diagnosed with both GIST and PM (7/2010-6/2020) at UC San Diego. Patient demographics, clinicopathologic features of both GIST and PM, somatic DNA mutations from CLIA-approved cancer panel sequencing, germline DNA variants, and survival outcomes were investigated.

Results: Over the last decade, 231 gastric GIST patients were evaluated at UC San Diego and 106 (45.9%) underwent resections at our institution. Of these 106 GIST patients, five (4.7%) also had PM. Overall, 40% were females and the median age at GIST diagnosis was 64 years old (range: 48-76) (**Fig. 1A**). The median GIST size was 8 cm (range 4.7 – 17.0) with median mitotic index of 2 mitoses per 5 mm^2 (range: 1 to 6). Eighty-percent of cases originated from either the lesser curve or the antrum of the stomach. Four patients (80%) had synchronous WDPM and one had MM. Additionally, three GIST+PM patients had other malignancies (renal cell carcinoma, *JAK2*^{V617F}-mutant polycythemia vera, Non-Hodgkins lymphoma, and prostate cancer) and/or benign tumors/lesions (meningioma and gallbladder adenomyoma). All five patients underwent R0 GIST resections and four patients had complete cytoreduction (CC0) with all 13 peritoneal cancer index (PCI) regions explored. The last patient had partial laparoscopic evaluation (6 regions visualized) with limited disease in the epigastrium and left upper quadrant (LUQ). Overall, the median PCI score was 1.5 in the WDPM patients (**Fig. 1B**). In contrast, the MM patient had a PCI score of 17. The PM distribution suggests a common site for GIST and PM co-occurrence, as epigastric disease was present in all 5 patients. Sequencing of four GISTs' DNA revealed somatic oncogenic *KIT exon 11* (N=2) or somatic *PDGFRA D842V* (N=2) mutations. Sequencing of the MM revealed somatic deleterious *BAP1* and *PBRM1* alterations. In addition, three of the five patients also had rare germline genomic alterations in homologous recombination DNA damage repair (HR-DDR) genes (i.e., *BAP1*, *PALB2*, and *RAD51D*), which were either variants of unknown significance (VUS) (N=1), variants with conflicting pathogenicity (N=2), or likely benign (N=1). Two additional germline VUS in other DNA repair-related pathways were also identified (*PRKDC*, *ZNF217*). Following resection, no patients experienced GIST recurrences at a median follow up of 7 months (range: 0.5-56). The WDPM patients had a median follow up of 5.5 months (range: 0.5-56) without evidence of recurrence while the MM patient developed a recurrence at 5 months postoperatively.

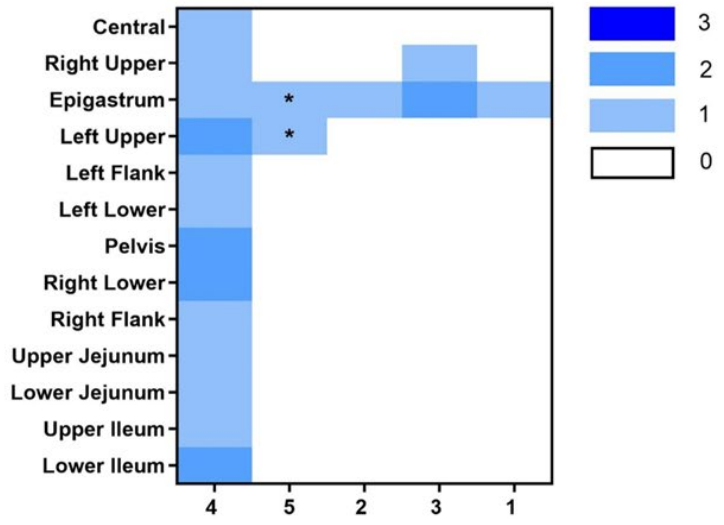
Conclusion: In the United States, the annual incidence of GIST is estimated at 7 cases per million and the annual incidence of PM is estimated at 2 cases per million. Herein, we report that nearly 5% of gastric GIST patients in our surgical series have PM, which is significantly higher than expected in the general population if these two diseases were independent events. The synchronous epigastric co-localization of both tumors with low PCI in four patients suggests the potential for an unrecognized relationship between these cancers, perhaps via potentially pathogenic germline alterations in HR-DDR. Taken together, the combination of GIST and PM represents an under-recognized co-occurrence often in patients with additional malignancies, suggesting a possible DNA repair-associated syndrome and/or symbiotic tumor relationship that deserve further investigation.

Figure 1

A


4
5
2
3
1
Patient
Demographics
57
76
64
71
48
Age
Sex
Race/Ethinicity
GIST
17
5
8
4.7
12
Size (cm)
1
1
2
3
6
MI (per 5 mm2)
Location
V559D
W577_ K558del
KIT (Exon 11)
PDGFRA D842V
PTCH1 (Hh pathway)
YYA1P1 (Hippo pathway)
STAG2 (Cohesion complex, DNA replication)
Mesothelioma
17
2
1
3
1
PCI
Histologic Subtype
BAP1 (Homologous recombination DNA repair)
PBRM1 (SWI/SNF-B chromatin-remodeling)
Germline (VUS) [HR-DDR]
BAP1 (Homologous recombination DNA repair)
PALB2 (Homologous recombination DNA repair)
RAD51D (Homologous recombination DNA repair)
Germline (VUS) [other]
PRKDC (DNA non-homologous end joining, NHEJ)
ZNF217 (HDAC complex)
Additional Cancers & Tumors
Renal Cell Carcinoma
Polycythemia Vera (JAK2 V617F)
Prostate Cancer
Gallbladder Adenomyoma
Non-Hodgkins Lymphoma
Meningioma
Sex
Female
Male
Race/Ethnicity
Caucasian (European)
Caucasian (Persian)
Asian/Pacific Islander
GIST Location
Fundus
Lesser Curvature
Antrum
Mesothlioma Histologic Subtype
Well Differentiated Papillary
Malignant
Genomic Alteration
Frameshift
Indel
Missense
Splice variant
Other
Unknown
Present

B


Central
Right Upper
Epigastrum
Left Upper
Left Flank
Left Lower
Pelvis
Right Lower
Right Flank
Upper Jejunum
Lower Jejunum
Upper Ileum
Lower Ileum
*
*
4
5
2
3
1
3
2
1
0

Poster #257 3465847

PEDIATRIC NON-MYOFIBROBLASTIC MESENCHYMAL NEOPLASMS WITH ALK AND ROS1 GENE REARRANGEMENTS

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Objective: Inflammatory myofibroblastic tumors (IMTs) are characterized histologically by a proliferation of spindle/epithelioid cells with myofibroblastic differentiation (immunohistochemical expression of smooth muscle actin [SMA]) and genetically by translocations involving receptor tyrosine kinase genes such as ALK and ROS1. Here, we describe 3 pediatric mesenchymal neoplasms with a proliferation of spindle/epithelioid cells without myofibroblastic phenotype that harbored translocations involving ALK (2 cases, including a novel translocation) and ROS1 (1 case).

Methods: Case 1. A 14-year-old girl underwent excision of a growing left neck mass noted a month earlier. Histologic examination showed a subcutaneous proliferation of spindle and epithelioid cells infiltrating a fibrous matrix. A large panel of immunohistochemical stains including SMA, calponin, ALK, and pan-cytokeratin was negative. There was weak cytoplasmic staining for ROS1.

Case 2. An 8-year-old girl underwent a biopsy of an intramuscular right flank mass at an outside institution. Histologic examination showed an infiltrative spindle cell neoplasm. The tumor cells were negative for SMA, but showed membranous and dot-like staining for CD34, nuclear and cytoplasmic staining for S100, and dot-like cytoplasmic staining for ALK.

Case 3. A newborn girl presented with a neck mass that was first noted at day of life 4. Needle core and incisional biopsies showed a proliferation of elongate and plump spindle cells with sparse inflammation. The tumor cells were negative for SMA, but showed weak nuclear and cytoplasmic staining for S100 and weak granular cytoplasmic staining for ALK.

Next generation sequencing. For all cases, total RNA was isolated from a representative FFPE block and library preparation was performed using Archer RNA Fusion v1 Custom FusionPlex® Kit (ArcherDx). The assay targets regions of 93 genes known to be associated with fusions in pediatric neoplasms. Massively parallel sequencing was performed on the Illumina MiSeq instrument. The analysis and fusion/variant detection was performed using the Archer Unlimited software (ArcherDx). RNA sequences used as references (hg19 (GRCh37)) are available on the NCBI website (http://www.ncbi.nlm.nih.gov/).

Results: Next generation sequencing identified a GOPC (exon 4) - ROS1 (exon 36) fusion in case 1, PLEKHH2 (exon 6) - ALK (exon 20) fusion in case 2, and a CLTC (exon 31) - ALK1 (exon 19) fusion in case 3. GOPC-ROS1 and CLTC-ALK fusions have previously been reported in a variety of pediatric and adult neoplasms, and PLEKHH2-ALK is a novel fusion.

Conclusion: We describe rearrangements of ALK and ROS1 genes in pediatric mesenchymal neoplasms composed of spindle/epithelioid cells that do not show myofibroblastic differentiation. Whether these neoplasms represent IMTs with aberrant loss of myofibroblastic phenotype or non-myofibroblastic mesenchymal neoplasms may be debated. Regardless, the absence of myofibroblastic differentiation should not preclude interrogation of pediatric spindle/epithelioid mesenchymal neoplasms for ALK/ROS1 gene rearrangements. Among the 3 gene fusions described here, PLEKHH2-ALK is a novel, previously unreported fusion.

Poster #258 3465855

UPDATED ANALYSIS OF GENETIC ALTERATIONS IN SARCOMA PATIENTS OF HISPANIC AND NON-HISPANIC ETHNICITY: ANALYSIS OF 174 PATIENTS, A SINGLE INSTITUTION EXPERIENCE

Emily E. Jonczak[2], *Caroline Hana*[1], *Andrea Espejo*[1], *Junaid Arshad*[1], *Philippos Costa*[1], *Priscila Barreto-Coelho*[1], *Konstantinos Sdrimas*[1], *Brianna Valdes*[1], *Gina D'amato*[1], *Jonathan Trent*[1]
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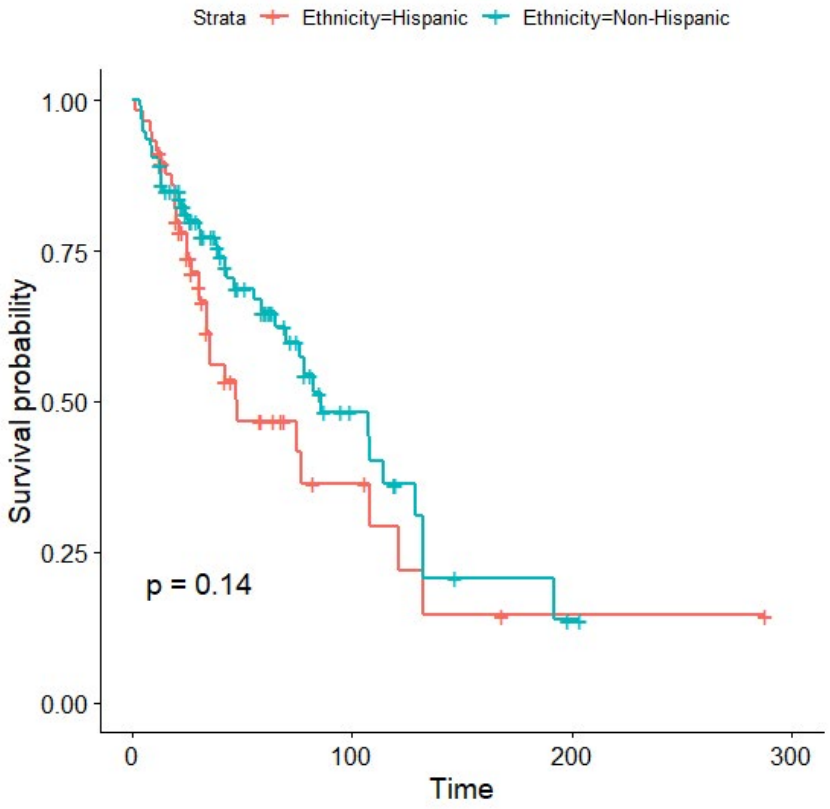
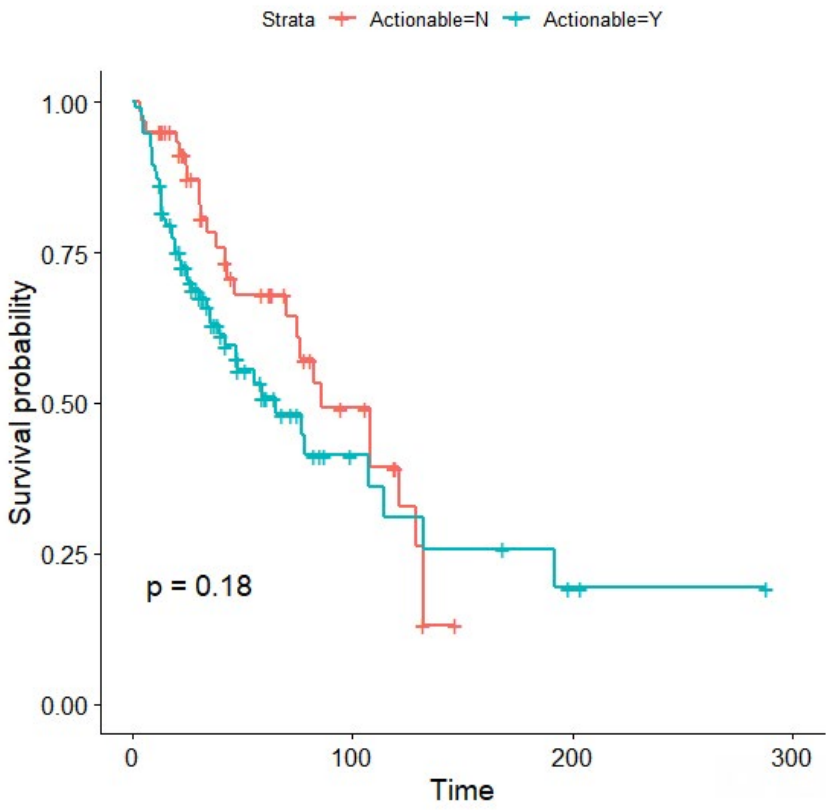
Objective: Over the last several decades, sarcomas have been managed with combinations of surgery, radiation, and standard cytotoxic chemotherapy. Despite this approach, metastatic sarcoma continues to be associated with poor prognostic outcomes. Advances in genetic sequencing techniques have allowed identification of genetic variability among this heterogeneous population of patients and prompted the development of novel targeted therapies. Our institution has a significant Hispanic population and previously presented the data on mutational variability between our Hispanic and non-Hispanic Sarcoma patients. Hispanics are the fastest growing major demographic group in the United States. Presently, according to the United States Census Bureau 2019 data, Hispanics make up 18.3% of the nation's population and continues to increase, while; genomic data for Hispanics remains grossly underrepresented. This genetically admixed population of patients as well as diverse trend in environmental exposures, lifestyle practices, and access to medical care offer opportunities to review the genetic variability and overall survival amongst this population. The purpose of this retrospective analysis is to expand upon the previously presented genetic variability, treatment approaches, and overall survival between our Hispanic and non-Hispanic Sarcoma patients.

Methods: Data for 174 patients was retrieved by chart review of electronic health records. Genomic sequencing data for all patients with a diagnosis of sarcoma from our institution was reviewed and kept in a HIPAA compliant database. The ESMO Scale of Clinical Actionability for molecular targets (ESCAT) and OncoKB precision oncology knowledge base were used to evaluate clinical relevance of various targets as defined by; Tier I: Targets used in clinical decisions, Tier II: Targets beneficial in patient population with additional data required, Tier III: Prior clinical benefit in other tumor types for similar targets, Tier IV: Pre-clinical evidence of actionability, Tier V: Evidence supporting co-targeting approaches, Tier X: Lack of evidence. Chart review was completed for each patient collecting demographic information, actionable mutations, treatment approach, and survival data.

Results: Out of 174 patients**,** 100 patients (57%) were females, 74 (43%) were males. The median age was 59 years (16-90). The majority of patients 110 (63%) were non-Hispanics, while 64 (37%) were of Hispanic ethnicity. All patients had biopsy proven sarcoma encompassing a wide range of histologies. Of the 174 patients, 108 (62%) had an actionable mutations. Among the patients with an actionable mutation, 62% were non-Hispanic and 38% were Hispanic. The most frequently observed actionable alteration was PTEN (Tier IV) seen in 13 of the 41 Hispanic patients (32%) and 21 of the 67 non-Hispanic patients (31%). Other actionable mutations observed included; PDGFRB (Tier I), CDK4 (Tier II), KRAS (Tier IV), NRAS (tier III), BRCA1 (Tier III), EGFR (Tier III), PTCH1 (Tier III), KIT (Tier I), BRAF (Tier III) and PIK3CA (Tier III). There was no difference in overall survival of Hispanic vs Non-Hispanic patient, p-value 0.14, however there was a trend towards poorer survival amongst hispanic patients, Figure 1. Firgure 2 shows the overall survival of patients with actionable mutations versus those with no actionable mutations. There is no statistical difference, p-value0 0.18, howvever trend towards improved survival amongst those with actionable mutations. Further subgroup analysis underway.

Conclusion: Advances in genetic sequencing have revealed the genetic variability amongst sarcomas of different histologies. Our study reveals a brief comparison of genetic landscape of Hispanic and non-Hispanic patients. It is notable that the majority of patients regardless of ethnicity had an actionable mutation. Our study elucidates that need for NGS amongst sarcoma patients in order to identify genetic variations and further develop target agents and clinical trials.


Strata
Ethnicity=Hispanic
Ethnicity=Non-Hispanic
1.00
0.75
0.50
0.25
0.00
Survival probability
p = 0.14
0
100
200
300
Time


Strata
Actionable=N
Actionable=Y
1.00
0.75
0.50
0.25
0.00
Survival probability
p = 0.18
0
100
200
300
Time

Poster #259 3465859

PREOPERATIVE RADIOTHERAPY IN LOWER EXTREMITY SOFT TISSUE SARCOMA TO REDUCE MAJOR WOUND HEALING COMPLICATIONS – THE ROLE OF NORMAL TISSUE DOSE REDUCTION

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Objective: The rate of major wound healing complications (MWC) in preoperative intensity modulated radiation therapy (IMRT) for lower extremity STS (leSTS) was 30.5% in a phase II trial that investigated normal tissue avoidance, particularly to the superficial tissues that would form the future surgical flaps, so-called 'flap-sparing' IMRT. We retrospectively compared this to a contemporaneous IMRT cohort where normal tissue avoidance was sought, but no specific attempt at flap-sparing was made, for MWC and outcomes.

Methods: We searched our institutional database for leSTS patients. MWC were defined as in the NCIC-CCTG SR 2 trial. All patients were treated with preoperative image guided IMRT followed by wide local excision of the tumour, 4-6 weeks after completion of RT. GTV, CTV definition was consistent between the 2 cohorts with a PTV expansion of 5 mm from CTV. All patients were treated with a dose of 50 Gy in 25 daily fractions. The phase II trial enrolled 59 evaluable patients and were treated with flap-sparing IMRT, as previously described (group A). A contemporary cohort of consecutive non-flap sparing IMRT patients (group B) was selected for comparison. Normal tissue avoidance in both groups was otherwise similar. Patients with angiosarcoma and desmoid tumors were excluded. All patients were assessed for MWC at least monthly until the 'final' assessment at 120 days postoperatively. Patients were then followed with clinical examination of the primary site and appropriate imaging for distant metastatic disease as needed every 3-6 months for 5 years and then annually to 10 years. Functional outcomes were collected using Toronto Extremity Salvage Score (TESS) and Musculoskeletal Society Score (MSTS). Multivariable logistic regression was used to compare major wound healing complications (MWC) between the two groups. Cumulative incidence of local recurrence considering death as a competing risk was calculated. T-test was used to compare functional outcomes at each follow up time between the groups.

Results: Group A included 52 patients treated between 2005 and 2009 and group B included 292 patients treated between 2005-2016. The median age of the patients was 57 years (range 18 -95); group A - 55 years, group B - 57 years. Median tumour size was 8.5 cm (range 1.3,37.4), (A= 9.5, B=8.2), 43 % had high grade disease (A= 44%, B= 43%), 83 % had negative margins and 17 % had positive margins post-surgical resection (A= 91% , B= 82 % with negative margins). The overall median follow-up was 4.2 years (A= 9, B= 3.9). MWC was 29% in Group A and 33% in Group B, (OR 1.22 p=0.56).
There was no difference in local control at 5 years with cumulative incidence of 7.7 % for Group A and 3.8% for Group B (p=0.38), distant metastasis occurred in 29.4 % of Group A and 30.8 % of Group B. There was no difference in the functional outcome scores using TESS, MSTS87, where preop TESS, TESS 3 month, TESS 1 year and TESS at 3 years for group A 85.8, 71.7, 89.1, 93.2 retrospectively, and for group B 85.7, 75, 89 and 91.8 retrospectively. Similarly for MSTS87 preop, 3 months, 1 year and 3 years for group A was 33, 29, 33, 35 and for group B 33, 29, 31, 33, respectively.

Conclusion: MWC were similar between the two cohorts and flap-sparing preoperative image-guided IMRT does not appear to offer an advantage over non-flap sparing techniques. Overall preoperative image-guided IMRT followed by surgery provides excellent rates of local control but offers marginal, if any, improvement in rates of MWC.

Poster #261 3465888

SUPERIOR MESENTERIC ARTERY BRANCHES AS A READOUT FOR PREDICTING FUTURE SMALL BOWEL LENGTH DURING ABDOMINAL AND RETROPERITONEAL LIPOSARCOMA RESECTIONS

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[1]*Department of Surgery, Division of Surgical Oncology, University of California, San Diego, La Jolla, California, UNITED STATES*

Objective: Short bowel syndrome (SBS) is defined by malabsorption of nutrients due to a significantly shortened length (less than 150-200 cm) of jejunum-ileum following small bowel resection (SBR). The risk of SBS is an important factor in determining resectability of abdominal/retroperitoneal tumors. Determining resectability of abdominal and retroperitoneal liposarcomas (LPS) can often be subjective, but one of the major factors defining resectability is involvement of the superior mesenteric artery (SMA) branches. We hypothesized that the number of uninvolved SMA branches correlates with sufficient preservation of small bowel length.

Methods: Under an IRB-approved protocol, we conducted a single surgeon retrospective analysis of surgically evaluated patients diagnosed with abdominal/retroperitoneal LPS (well and/or dedifferentiated) at UC San Diego from May 2012 to May 2020. Patient demographics, operative management, LPS clinicopathologic factors, analysis of preoperative cross-sectional CT/MRI images for SMA branches uninvolved by disease and resected bowel length were investigated.

Results: Fifty-two LPS patients were eligible for inclusion. The median age was 59.5 (mean 59.1±14.5) and 21 (40.4%) were women. Thirty-five (67.3%) patients underwent total gross resection at UC San Diego. Of these 35 LPS patients, the median tumor size was 18.3 cm (mean: 21.2±12.9; range: 3.6-51.5 cm). The histological subtypes were 37.1% dedifferentiated, 25.7% well differentiated, 25.7% mixed, 8.6% pleomorphic, and 2.9% round cell LPS. Moreover, 45.7% were G3, 22.9% were G2, 20% were G1, and 11.4% were ungraded. There was no significant intergroup differences between SBR, Col, and No SBR/Col groups in terms of histological subtype, grade or size (P=NS). Twelve (34.30%) had concomitant small bowel resections (SBR) with/without colon resections, 6 (17.1%) had only colectomies (Col), and 17 (32.7%) had tumor resections without small bowel or colectomies. Both the SBR and Col patients had a median of 11 uninvolved SMA branches (mean: 10.9±2.1 vs mean: 11±1.7). In contrast, the patients that underwent total gross resections without SBR or Col had a median of 15 uninvolved SMA branches (mean: 14.5±3.6; P<0.005 vs SBR or Col). We next assessed the length of small bowel versus colon resected in these patients. For 92.3% (12/13) cases with >14 uninvolved SMA branches, we resected the tumors while preserving 100% small bowel length. In contrast, 11 of 22 (50%) patients with ≤14 uninvolved SMA branches had SBRs (resected length range: 11.6 - 69 cm). Moreover, having ≤14 uninvolved branches increased the odd ratio of SBR by 12 (95% CI 1.3-108.8, P<0.05). Finally, on bivariate analysis, fewer uninvolved SMA branches (r_s = -0.60, P<0.01) or increasing tumor size (r_s=0.37, P=0.03) correlated with increased tendency for SBR.

Conclusion: This represents the first objective approach for predicting the need for small bowel resection in abdominal/retroperitoneal LPS based on the number of uninvolved SMA branches on cross sectional imaging. Further validation of this approach in a larger series is warranted to define a strategy for improving the granularity of defining abdominal/retroperitoneal liposarcoma resectability.

Poster #262 3465890

THE IMPACT OF RADIATION THERAPY ON SURVIVAL IN MYXOID LIPOSARCOMA

David L. Kerr[1], *Alexander L. Lazarides*[1], *Preet Patel*[3], *Mark M. Cullen*[3], *Sneha Rao*[1], *Marcelo Cerullo*[2], *Dan G (Trey) Blazer*[2], *Brian E. Brigman*[1], *Julia D. Visgauss*[1], *William C. Eward*[1]
[1]*Orthopedic Surgery, Duke University Hospital, Durham, North Carolina, UNITED STATES;* [2]*General Surgery, Duke University Hospital, Durham, North Carolina, UNITED STATES;* [3]*Duke University School of Medicine, Durham, North Carolina, UNITED STATES*

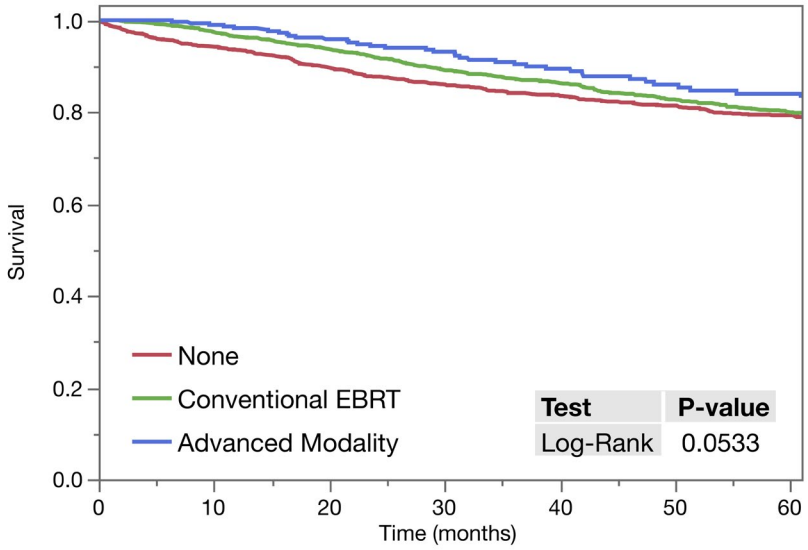
Objective: Myxoid liposarcoma (MLS) is a malignant tumor characterized by the FUS-DDIT3 translocation, and is typically is regarded as radio- and chemo-sensitive with low rates of local recurrence and metastasis compared to other liposarcoma subtypes (Crago and Dickson 2016). Radiation therapy (RT) is consistently used for treatment of MLS – and local effects on the tumor are typically pronounced – yet numerous recent studies found no significant improvement in overall survival with radiation therapy (Chowdhry, Goldberg et al. 2018, Wu, Qian et al. 2019, Zheng, Yu et al. 2019, Amer, Congiusta et al. 2020). As these studies have largely been performed at single institutions or used smaller databases and thus are limited in size, we investigated the National Cancer Database (NCDB) to determine the role for RT in MLS.

Methods: We retrospectively reviewed 3,811 patients with a diagnosis of MLS in the National Cancer Database (NCDB) from 2004 through 2015. After inclusion and exclusion criteria were met, 3,263 patients remained. Univariate analysis by Pearson Chi-Square method assessed differences between cohorts. Survival differences between patients who received no radiation or different modalities of radiation (conventional EBRT or advanced modalities) were assessed using the Kaplan-Meier method. Multivariate analysis by proportional hazards regression was used to assess patient, tumor and treatment variables as independent predictors of survival.

Results: Myxoid liposarcomas were predominantly located in the extremities (76% vs. 11% in pelvis, 13% other axial locations). The 5-year survival for entire cohort was 79%. 1,766 (54%) patients received radiation therapy, of which 1467 (83%) received conventional EBRT and 299 (17%) received advanced modalities. IMRT constituted the majority of advanced modality RT with 290 patients, as well as 1 stereotactic radiosurgery (SRS), 1 proton-beam therapy (PBT), and 1 neutron-beam therapy. Patients receiving conventional EBRT received a mean of 50 Gy compared with 51 Gy for advanced modalities ($p=0.047$). Compared to no radiation, patients who received neoadjuvant radiation were less likely to have positive margins (10% vs. 17%, $p<0.001$). 5-year survival was 80% for patients who received conventional EBRT and 84% for advanced modality radiation (Log-rank $p=0.0533$). In multivariate analysis, RT was associated with significantly improved survival compared to no radiation (HR 0.78 [0.64-0.96], $p=0.019$), and advanced modality RT also demonstrated a survival benefit compared to conventional EBRT (HR 0.65 [0.47-0.90], $p=0.010$). MLS was more predominant in males (60%), with female sex conferring an independent survival advantage in multivariate analysis (HR 0.77 [0.65-0.90], $p<0.001$). Comorbidities, insurance status, metastases, as well as tumor size, grade, and depth were all significant predictors of survival (Figure 2). While surgical resection conferred a significant survival advantage (HR 0.43 [0.34-0.55], $p<0.001$), there was no significant difference in survival between positive and negative margin status ($p=0.936$). Race, facility type, and chemotherapy were also not predictive of survival (Figure 2).

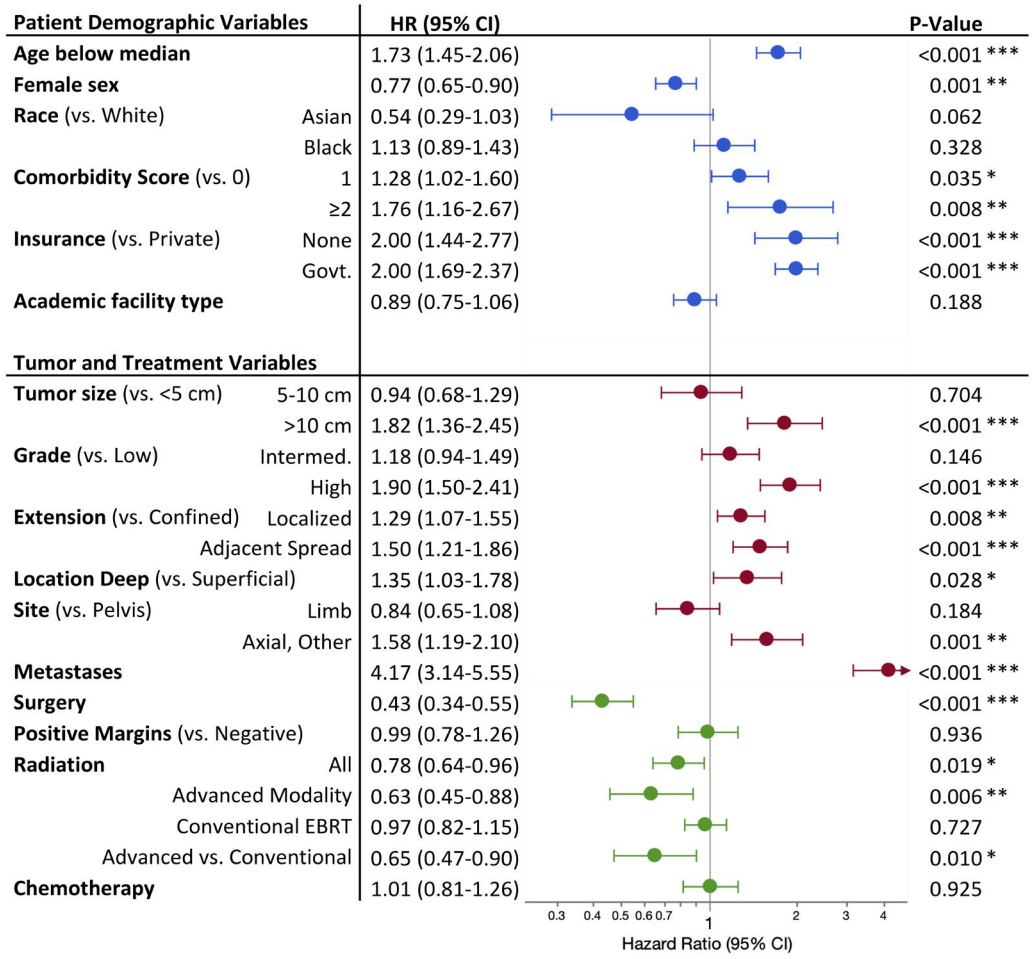
Conclusion: Radiation therapy is already commonly used to treat patients with MLS in conjunction with surgical resection. Contrary to recent prior studies, we found that RT did confer a statistically significant survival advantage. Furthermore, the use of advanced modalities such as IMRT significantly improved survival compared to conventional EBRT, and further studies may be useful to determine their utility in neoadjuvant treatment of this radiosensitive tumor, as well as post-operatively for treatment of positive margins or resection of high-grade or locally aggressive tumors.

5-Year Survival of Myxoid Liposarcoma Patients by Radiation Modality. Kaplan-Meier survival of patients with myxoid liposarcoma revealed a 5-year survival rate of 79% in those who received no radiation, compared with 80% who received conventional EBRT and 84% wh received advanced modality radiation. The survival difference was not statistically significant (Log-rank p=0.0533).



Predictors of Survival in Myxoid Liposarcoma

Patient, tumor and treatment variables were assessed for their influence on unplanned readmissions by multivariate proportional hazards regression. Hazard ratios and 95% confidence intervals are shown and demonstrated in the forest plot. P-values provided with statistical significance noted as *p<0.05, **p<0.01, ***p<0.001.



Poster #263 3465898

DOES ATTACHMENT STYLE (RELATIONSHIP STATUS) IMPACT OUTCOME IN ADULTS WITH SARCOMA?

Abha A. Gupta[1], *Madeline Li*[1], *Nicole Byers*[1], *Caroline Rodrigues*[1], *Kupere Pathmanathan*[1], *Osvaldo Espin-Garcia*[1], *Jay Wunder*[1], *Peter Ferguson*[1], *Kim Tsoi*[1], *Rebecca Gladdy*[1], *Carol J. Swallow*[1], *Savtaj Brar*[1], *Peter Chung*[1], *Charles Catton*[1], *David Shultz*[1], *Philip Wong*[1], *Albiruni Razak*[1], *Hagit Peretz*[1], *Bob Maunder*[1], *Anthony Griffin*[1], *Jon Hunter*[1]
[1]*Princess Margaret, Toronto, Ontario, CANADA*

Objective: A diagnosis of cancer is often the most significant event in a person's life, and social relationships at the time of diagnosis may influence their experience of illness and even survival. Unmarried patients are at significantly higher risk of presentation with metastatic cancer, under-treatment, and death resulting from their cancer. One candidate for how marital status could influence cancer outcome is 'attachment style' (AS), which refers to a person's 'default' attitudes and strategies for relating to others, encompassing interpersonal qualities such as confidence in self and trust in others. AS has been shown to be correlated with aspects of stress physiology, which could reasonably be understood to be relevant for disease progression. We sought to perform an exploratory analysis on the impact of marital status on sarcoma outcome and hypothesize that outcome will be mediated by patients' anxiety, depression and AS.

Methods: We identified consecutive sarcoma patients diagnosed between Jan 2012–June 2018 from our institutional prospective database who had completed pre-surgery patient-reported outcome measures for physical symptoms (ESAS-r), as well as distress risk factors such as living arrangements, personal and family psychiatric history. All factors are captured in the prospective Distress Assessment & Response Tool database, which prompts patients to complete survey at each clinic visit. The majority of patients also completed a 12-point questionnaire on Relationship experiences (Experience in Close Relationships, Table 1); mean scores were calculated. Overall survival (OS) was estimated using the Kaplan-Meier (KM) method. Differences in levels of depression and anxiety between married and non-married were compared using Fisher exact test. Cox proportional hazards regression model was used to compare differences in OS.

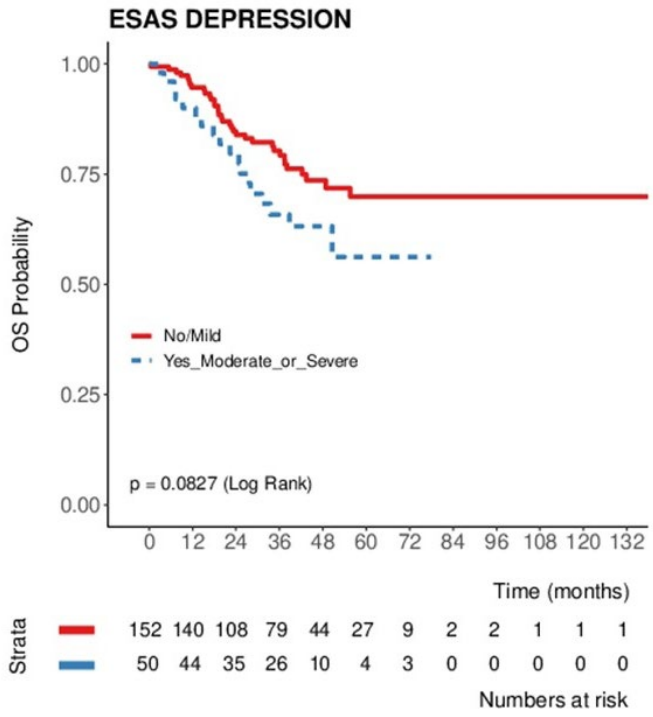
Results: Of 321 patients, 155 (48%) were women. Median age was 58 years (18-91) at the time of surgery. Distribution of sarcoma site is as follows: 51 (15%) bone; 207 (64%) extremity soft tissue sarcoma (STS); and 63 (19%) retroperitoneal STS. 301 (94%) patients were without metastases at baseline. At the time of primary surgery, 242 (75.4%) were married and 76 (24%) were non-married (35 (11%) previously married, 41 (13%) single). PHQ-9 and GAD-7 were similar between married and non-married individuals whereas relationship experiences differed between the 2 groups (data not shown). In univariable analysis, certain ECR items impacted OS (Table 1), however attachment style per se did not (p=n.s.). In addition, 2-year KM estimates for OS were 84% for those patients reporting no/mild depression, compared to 80% for those reporting moderate/severe depression (p=0.08). Marital status and level of anxiety did not impact OS in multivariable analysis, however, ESAS depression (HR 2.5, 95%CI 1.2-5.5, p=0.02) was statistically significant for OS.

Conclusion: Marital status does not impact OS; however, there is an association between depression and overall survival in adults with sarcoma. Ongoing efforts will focus on determining if AS mediates that relationship.

Table 1. Experience in Close Relationships: Impact on OS

For some people, experiences in close relationships can be an important part of living with an illness. The 12 statements below concern how you generally feel in emotionally close romantic relationships. We are interested in how you generally experience relationships, not just in what is happening in a current relationship. Respond to each statement by indicating how much you agree or disagree with it.	Strongly Disagree	….	Strongly Agree	Impact on OS
It helps to turn to my romantic partner in times of need.				0.42
I need a lot of reassurance that I am loved by my partner.				0.71
I want to get close to my partner, but I keep pulling back.				0.24
I find that my partner(s) don't want to get as close as I would like				0.003
I turn to my partner for many things, including comfort and reassurance.				0.56
My desire to be very close sometimes scares people away.				0.005
I try to avoid getting too close to my partner.				0.11
I do not often worry about being abandoned.				0.081
I usually discuss my problems and concerns with my partner.				0.27
I get frustrated if romantic partners are not available when I need them.				0.045
I am nervous when partners get too close to me.				0.093
I worry that romantic partners won't care about me as much as I care about them.				0.002

Figure 1. OS and Depression in Adults with Sarcoma



Poster #264 3465900

WHAT IS THE LIKELIHOOD OF NON-PULMONARY METASTASIS OCCURRING IN THE ABSENCE OF LUNG METASTASIS IN BONE AND SOFT TISSUE SARCOMA? A NESTED CASE CONTROL STUDY FROM A REFERRAL SARCOMA CENTER

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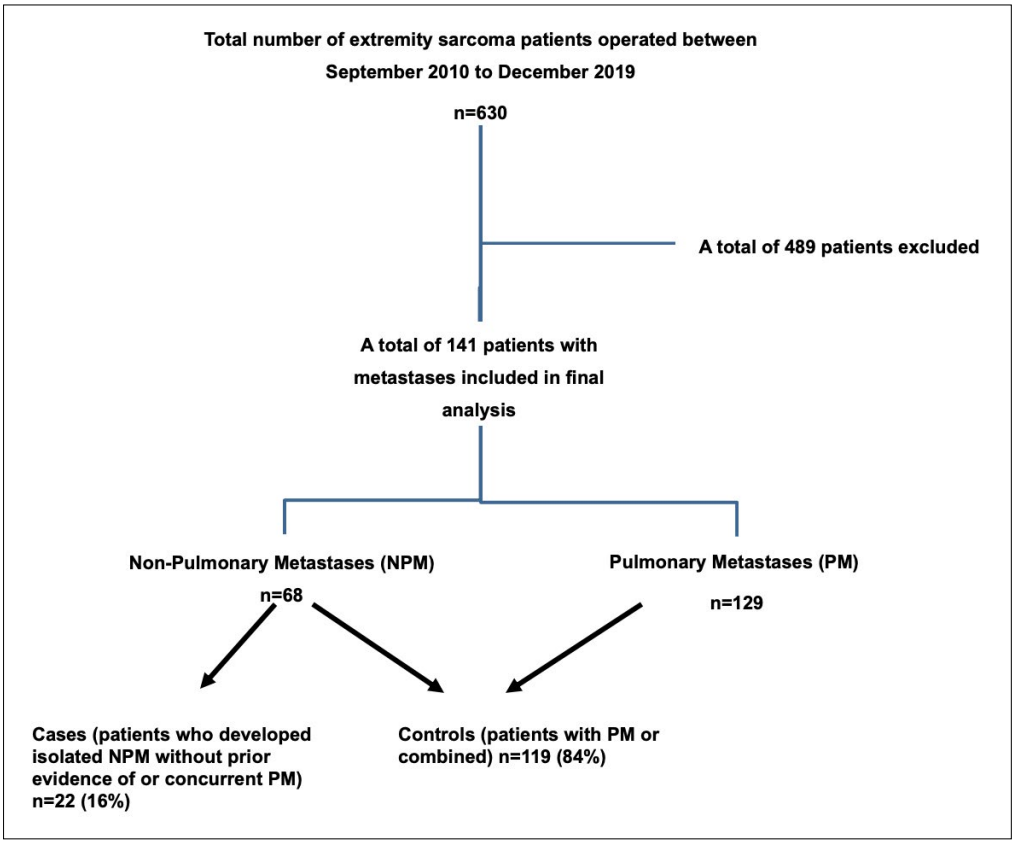
Objective: To measure the incidence of isolated Non-Pulmonary Metastases (NPM) in bone and soft tissue sarcoma patients, to determine if NPM occur in isolation or if they are predicted by the presence of synchronous or prior pulmonary Metastases (PM), and to identify the predicting factors for NPM. PM in bone and soft tissue sarcomas have a drastic effect on overall survival. Non-pulmonary metastases (NPM) (Visceral, nodal, and osseous) are rare and associated with poorer prognosis. Although the accepted clinical practice is to obtain chest imaging for sarcoma surveillance, there is paucity in literature on whether imaging of the lung alone is enough to identify the presence of overall metastasis in the body.

Methods: Investigators identified patients who developed NPM from an ongoing cohort of bone and soft tissue sarcoma patients. We retrospectively collected patient characteristics and tumor clinicopathological variables. Our population of interest was patients who developed isolated NPM without prior evidence of or concurrent PM. PM recognized within 3 months of NPM was considered concurrent. We analyzed the background characteristics and predicting factors. Non-parametric analysis was used followed by subgroup analysis and results were reported in-line with the criteria of Strengthening The Reporting of Cohort Studies in Surgery (STROCSS).

Results: From the overall cohort of 630 extremity sarcoma patients treated between September 2010 to December 2019, the overall incidence of metastasis was 141 (22%). Out of the 141 patients with metastasis, 129 (91%) patients had PM while 68 (48%) had NPM. Twenty-two patients (16%) demonstrated isolated NPM; 7 later developed PM. The most common site for NPM was bone, followed by abdominal viscera and lymph nodes. Malignant peripheral nerve sheath tumor, angiosarcoma, rhabdomyosarcoma, synovial sarcoma, and myxoid liposarcoma were more likely to develop isolated NPM than other subtypes of soft tissue sarcoma (OR 12, 95% CI 3-46, $p<0.001$). Interestingly, isolated NPM were 3 times more likely to metastasize to a single site compared to the control group (PM or combined) (OR 3.2, 95%CI 1.1-10).

Conclusion: Patients who develop isolated NPM, without prior or concurrent PM, are rare and demonstrate a predilection towards some subtypes of extremity sarcoma. Patients diagnosed with malignant peripheral nerve sheath tumor, angiosarcoma, rhabdomyosarcoma, synovial sarcoma, and myxoid liposarcoma have a higher incidence of isolated NPM and may require more than simple chest imaging for comprehensive surveillance. They are more likely to develop oligometastatic metastatic, which may be amenable for surgical excision.



Histology subtypes and anatomical location among cases (isolated non-pulmonary metastasis) and controls (pulmonary metastasis or combined).

Histological Dx	Total n (%)	Cases n (%)	Controls n (%)
Osteosarcoma	25 (18%)	2 (9%)	23 (19%)
Malignant Nerve sheath	7 (5%)	3 (14%)	4 (3%)
Solitary fibrous	1 (%)	0	1 (1%)
Epithelioid sarcoma	2 (1%)	0	2 (2%)
Clear cell sarcoma	2 (1%)	0	2 (2%)
Malignant GCT	1 (1%)	0	1 (1%)
Angiosarcoma	1 (1%)	1 (5%)	0
Sarcoma, NOS	3 (2%)	1 (5%)	2 (2%)
Rhabdomyosarcoma	3 (2%)	2 (9%)	1 (1%)
Chondrosarcoma	16 (11%)	5 (23%)	11 (9%)
Extra Skeletal sarcoma	1 (1%)	0	1 (1%)
Alveolar soft part	2 (1%)	0	2 (2%)
Ewing sarcoma	11(8%)	3 (14%)	8 (7%)
UPS	32 (23%)	2 (9%)	30 (25%)
Fibrosarcoma	1 (1%)	0	1 (1%)
Myxoid Liposarcoma	8 (6%)	2 (9%)	6 (5%)
Myxofibrosarcoma	8 (6%)	0	8 (7%)
Synovial sarcoma	6 (4%)	1 (5%)	5 (4%)
Leiomyosarcoma	11 (8%)	0	11 (9%)
Location			
Lower Limb	110 (78%)	15 (68%)	95 (80%)
Upper Limb	7 (5%)	3 (14%)	4 (3%)
Axial/Girdle	24 (17%)	4 (18%)	20 (17%)
Total	**141 (100%)**	**22 (100%)**	**119 (100%)**

Poster #265 3465904

SURGICAL MANAGEMENT REMAINS THE BEST PREDICTOR OF SURVIVAL: LESSONS FROM THE NATIONAL CANCER DATABASE (NCDB) IN DESCRIBING CHARACTERISTICS, MANAGEMENT, AND OUTCOMES FOR PATIENTS WITH CHONDROSARCOMA

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Objective: Chondrosarcoma represents a significant percentage of all primary osseous tumors. In the last decade, there has been significant development of new therapies to address the growing burden of oncological bone disease, however, there are few large-cohort, longitudinal studies of long-term survival and treatment outcomes in chondrosarcoma patients with the majority of studies being limited to a single institution or with diverse tumor histology. Thus, the current study used the large, robust National Cancer Database (NCDB) to investigate risk factors and treatment modalities correlated with the likelihood of mortality for patients diagnosed with primary osteochondroma.

Methods: NCDB datasets were queried for patients undergoing treatment for chondrosarcoma between 2004-2015. Primary tumor location was then used to separate patients under the following categories: axial, appendicular, and other. Demographic, treatment, and long-term survival data were then calculated for each of these groups at the one-, five-, and ten-year time points post-operation. Multivariate Cox analysis and Kaplan-Meier survival curves were generated to further elucidate trends in the long-term survival of patients at any point following their procedure.

Results: 5,329 chondrosarcoma patients were identified, of which 1,616 were axial and 2,686 appendicular. Multivariate Cox analysis revealed that among the axial cohort, the likelihood of death rose significantly based on patients' age category or distant metastases at presentation (Incident Rate Ratio (IRR)=3.12, $p<0.001$), but significantly decreased with surgical treatment (IRR=0.356, $p<0.001$) and surgical treatment with radiation (IRR=0.373, $p<0.001$).

In the appendicular cohort, the likelihood of death significantly increased with age category and distant metastases at presentation (IRR = 6.794, $p < 0.001$) and significantly decreased for female sex (IRR=0.692, $p<0.001$), and surgical treatment (IRR=0.533, $p<0.001$).

Kaplan-Meier survival analysis shows that survival is significantly worse in the axial cohort ($p<0.001$) and for patients with distant metastases at presentation ($p<0.001$). Survival has not significantly increased between older and more recent years ($p=0.742$).

Conclusion: Surgical management remains the best predictor of survival for both axial and appendicular chondrosarcomas, although there have been no significant advancements in survival over the last eleven years despite advances in treatment modalities. Presence of distant metastases is a significant, poor prognostic sign as is axial involvement most likely due to wide spread disease and difficulty in ease of resection.

Figure 1A: Long-term survival of patients in the axial, appendicular, and other cohorts ($p < 0.001$).

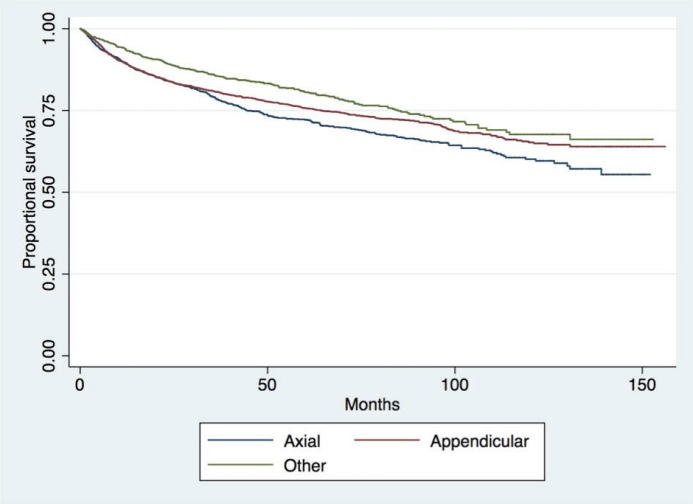


Figure 1B: Long-term survival of patients in the three different era groups ($p = 0.742$).

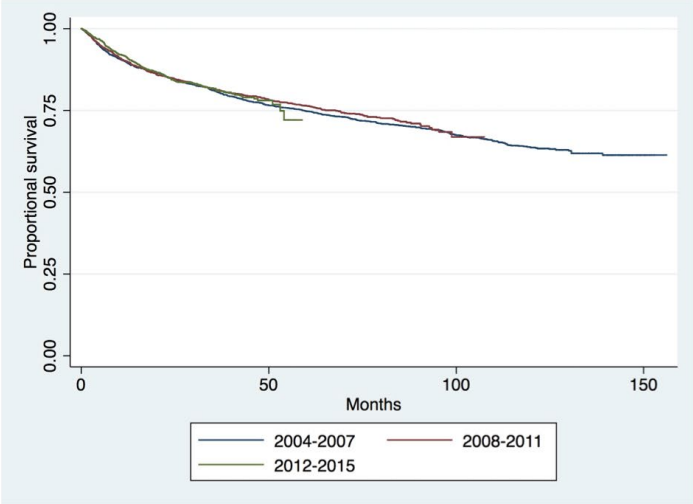
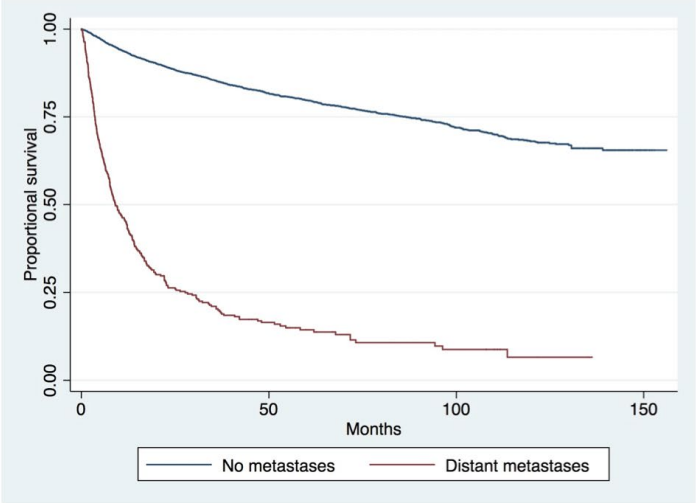


Figure 1C: Long-term survival of all patients with and without distant metastases at the time of presentation ($p < 0.001$).



Poster #266 3465916

WHAT ARE THE PREDICTORS OF READMISSION AND SHORT TERM MORTALITY IN CHONDROSARCOMA?

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Objective: Chondrosarcoma remains a challenge for optimal surgical management. These often undergo large and complicated surgeries and are at risk for readmission. The Centers for Medicare & Medical Services (CMS) has placed an emphasis on improving health care efficiency while cultivating excellent patient outcomes. While there have been advances elsewhere in Orthopaedics, there is limited data available to inform short term outcomes for patients with chondrosarcoma. The goal of this study was to identify factors independently associated with 30-day readmission and short term (90 day) mortality for patients undergoing surgical resection of chondrosarcoma.

Methods: We retrospectively reviewed all patients (n = 5400) undergoing surgical resection of primary osteosarcoma in the National Cancer Database (NCDB) from 2004 through 2015. Inclusion criteria included all patients that had data on readmission. of these patients, 4919 had data on 90-day mortality for analysis. Univariate associations of demographics and risk factors with readmission and short-term mortality were assessed with chi-squared and logistic regressions. A multivariate logistic regression was used to determine the variables independently correlated with readmission and short-term mortality while controlling for potential confounders.

Results: We found that there were 172 readmissions (3.2%), and there was no significant change in readmission rates over this time (p = 0.830). After controlling for confounders, lower income (1.5, p=0.012), major amputation (HR 2.9, p<0.001) and metastatic disease at presentation (HR 2.3, p=0.025) were independently associated with increased risk of unplanned readmission. Age, insurance status, grade, tumor size and surgical margins were not associated with risk of readmission. 32 patients died within 90 days of their surgery (0.7%); there were no significant changes in short-term mortality over the study period (p=0.475). Age (HR 1.04, p=0.001), higher grade (HR 1.6, p=0.002), and metastatic disease at presentation (HR 7.1, p<0.001) were independently associated with increased risk for short term mortality, as were positive surgical margins (HR 2.9, p=0.001) and higher comorbidity burden (HR 2.8, p=0.012). Radiation therapy was associated with decreased risk of short-term mortality (p<0.001). Neither insurance status, tumor location nor resection type were associated with risk of short-term mortality.

Conclusion: We identified several associations with unplanned readmission in chondrosarcoma: income, surgery type, and metastatic disease were independently associated with readmission rates. Age, grade, margin status, metastatic disease and comorbidity burden were independently associated with short term mortality. These features should be considered and taken into account when anticipating short term outcomes.

Poster #267 3465927

PROBING THE THERAPEUTIC LANDSCAPE OF CHONDROSARCOMA WITH INTEGRATED CHEMICAL SCREENING

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Objective: Chondrosarcoma is the second most common primary bone malignancy. Localized chondrosarcoma is treated with wide surgical excision; however, there remains no effective systemic treatment for patients with metastatic disease. Furthermore, our understanding of the drivers of disease progression are lacking. In this study, we conducted a high throughput drug screen using a novel approach to analysis. Our aim was to identify drugs with general effectiveness against chondrosarcoma, as well as those with differential sensitivity in metastatic vs non-metastatic cell lines. We believe that the targets of these drugs may not only represent potential therapeutics but may also elucidate critical aberrant pathways responsible for tumor aggressiveness and metastatic potential.

Methods: We conducted high-throughput drug screening with three different libraries (OICR Kinase Inhibitor, Selleck and Prestwick) on five patient-derived cell lines with known clinical behavior. Drug libraries included drugs known to be active against cancer as well as other diverse compounds with known bioavailability and safety in humans. A total of 2,565 drugs were tested on five cell lines, including two metastatic, and three non-metastatic. Cells were plated in 384-well format and treated with drug for 60hrs, after which cell viability was assessed with Alamar Blue. Cells were treated in triplicate and median viability was assessed, in addition to calculation of B-scores (based on Tukey's median polish methods) to account for positional variability of the plates and normalize drug activity to a percent score. Drug hits were identified using median activity scores as well as values +/- 3SD from the mean B-score. Additionally, protein drug target data from these drug screens was extracted and drugs were sorted into clusters using an Unsupervised Clustering and Dimensional Reduction (UMAP) technique. Drugs were clustered using k-means into groups based on similarities in pathways and viability metrics. Based on these results, protein target information for two clusters with the most clinically significant activity were entered into the STRING and KEGG databases to visualize protein-protein interaction and identify high level molecular function and pathways.

Results: Our drug screen identified four drugs with differential sensitivity in metastatic cell lines as compared to non-metastatic: IKK-16, Dabrafenib Mesylate, Sepantronium Bromide, and Camptothecin. The targets of these drugs are IKK1/2, BRAF, Survivin, and TOP1, respectively. Unsupervised Clustering and UMAP revealed six clusters [Figure 1], two of which (Clusters 1 and 4) included drugs that resulted in a significant reduction in cell viability. Cluster 1 contained drugs with effectiveness across all chondrosarcoma cells lines tested, while Cluster 4 represented drugs with increased effectiveness in metastatic cell lines [Figure 2]. Our four individual drug hits were also identified in Clusters 1 and 4 using the UMAP clustering method. Clusters 1 and 4 shared many common protein targets including CDK, mTOR/PI3K/Akt, Raf, PDGFR, VEGFR, SRC, HDAC, and JAK/STAT [Figure 3]. KEGG pathways identified PI3K-Akt signaling pathway, cell cycle, cellular senescence, and EGFR tyrosine kinase inhibitor resistance within the top 10 molecular functions in both clusters.

Conclusion: Our drug screen has identified four potential drugs warranting further investigation for the treatment of chondrosarcoma. Moreover, our novel analytical approach has identified multiple pathways that not only may serve as potential therapeutic targets but may also represent pathways critical to disease progression and metastasis in chondrosarcoma. Overall, this novel clustering and UMAP approach illuminated much more information than traditional means of analyzing drug screen data.

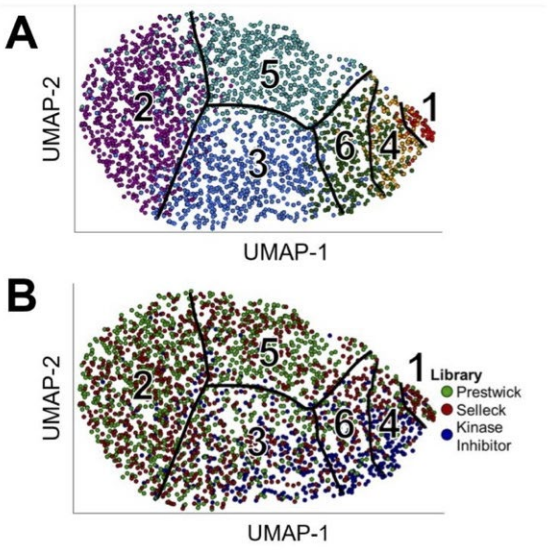

Figure 1. (A) UMAP projection and distribution of pharmaceuticals by cluster and library. (A) We identified 6 clusters that decreased in size along UMAP-1. **(B)** Members of the Prestwick, Selleck, and Kinase Inhibitor libraries were well-distributed among clusters.

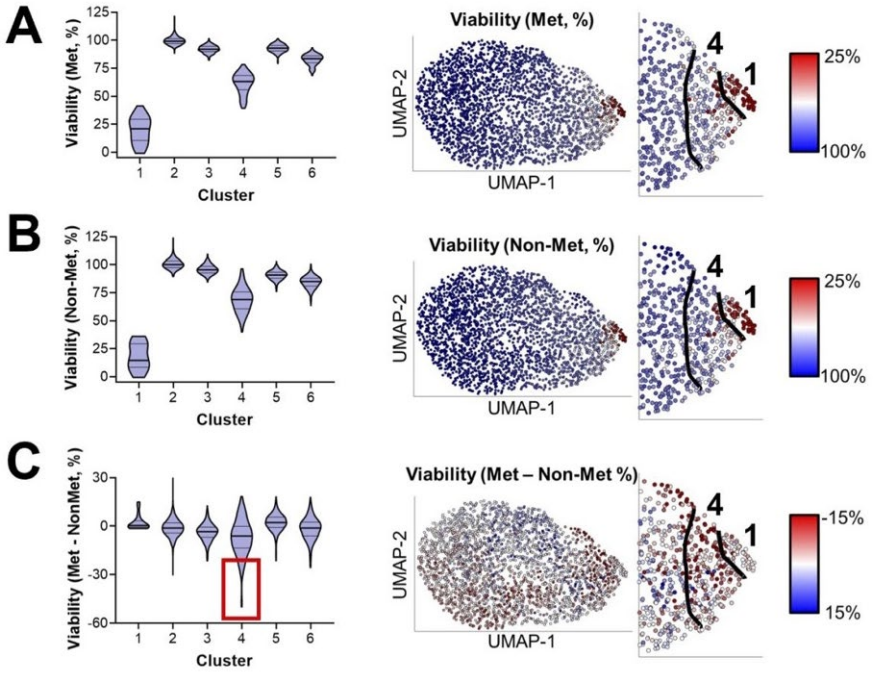

Figure 2. Viability of metastatic and non-metastatic cell lines by cluster. **(A and B)** Pharmaceuticals that that were most effective against metastatic and non-metastatic cell lines (red) were predominantly located in clusters 1 and 4. **(C)** Pharmaceuticals that were more effective against metastatic cells (red box on violin plot, dark red color on UMAP projection) were located in cluster 4. (scale: negative is more effective versus metastatic cells)

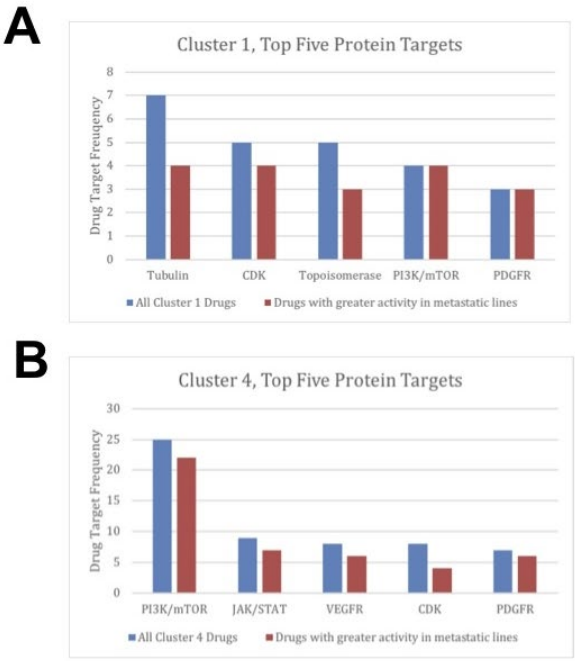

Figure 3. Top five most frequently targeted proteins from drugs in **(A)** Cluster 1: tubulin, CDKs, topoisomerase, PI3K/mTOR, and PDGFR and **(B)** Cluster 4: PI3K/mTOR, JAK/STAT, VEGFR, CDK, PDGFR.

Poster #268 3465928

RACIAL DISPARITIES BY HISTOLOGY FOR SARCOMAS OF SOFT-TISSUE AND BONE

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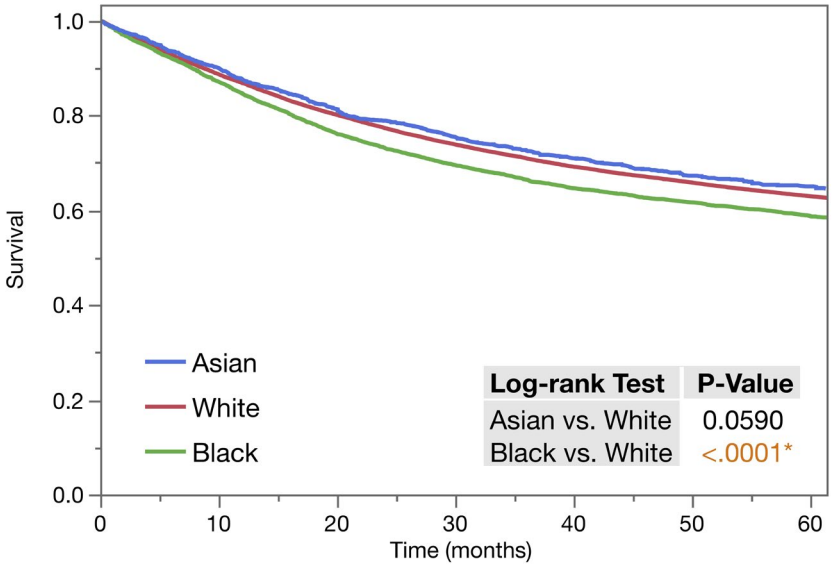
Objective: Chromosomal translocations and somatic mutations are known to be predisposing elements for the development of many sarcomas of soft-tissue and bone, yet patient survival has been shown to also depend on a number of demographic and treatment factors. Race has previously been shown to impact medical care and cancer outcomes; whether this is predominantly attributable to genetic or external factors is not yet known in sarcomas. Here we examined the impact of patient race on survival in the setting of various soft-tissue and bone sarcomas.

Methods: We retrospectively reviewed 123,244 patients with diagnoses of sarcoma of the soft-tissue or bone in the National Cancer Database (NCDB) from 2004 through 2015. After inclusion and exclusion criteria were met, 62,260 patients remained. Kaplan-Meier analysis and log-rank tests were used to compared survival between races. Multivariate analysis by proportional hazards regression was used to assess patient, tumor and treatment variables as independent predictors of survival. To more clearly distinguish the influence of race on survival across the various sarcoma types, an interaction of Race*Histology was also included in the model.

Results: The study population included 51,720 (86%) patients who identified as Caucasian, 6,722 (11%) as African-American, and 1,818 (3%) as Asian. The 5-year survival rates were 65% for Asian and 59% for African-American, compared with 63% for Caucasian (log-rank p-values for overall survival compared to White race were p=0.0590 and p<0.0001, respectively). Compared to Caucasian patients, African-American patients were less likely to have private insurance (48% vs. 55%, p<0.001) or above-median income (37% vs. 62%, p<0.0001). African-American patients also had an increased average time between diagnosis and any treatment (25 vs. 20 days, p<0.0001), surgery (44 vs. 37 days, p<0.0001), and chemotherapy (48 vs. 45 days, p=0.0027). There was no significant difference in average time between diagnosis and radiation therapy (88 vs. 86 days, p=0.274) There was no significant difference in time between diagnosis and radiation (88 vs. 86 days, p=0.274). In a multivariate analysis including various patient, demographic, and tumor variables, African-American race was associated with significantly worse survival compared to White race for 4 of 8 histologic groups: Ewing sarcoma (HR 1.41 [1.09-1.82], p=0.008), synovial sarcoma (HR 1.21 [1.03-1.42], p=0.024), leiomyosarcoma (HR 1.13 [1.02-1.24], p=0.021), and "STS, Other" which included spindle, giant cell, small cell, epithelioid, and undifferentiated sarcomas (HR 1.14 [1.04-1.25], p=0.006). Black race was associated with improved survival in rhabdomyosarcoma (HR 0.81 [0.7-0.95], p=0.008). Asian patients did not demonstrate significant survival differences across histologies compared to Caucasian patients, other than for fibrosarcoma (HR 0.72 [0.57-0.92], p=0.008).

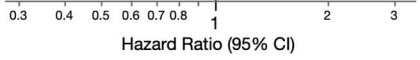
Conclusion: Race was associated with variations in survival for both soft-tissue and bone sarcomas in a multivariate analysis that included other tumor or demographic characteristics known to independently influence survival, such as income and insurance. African-American patients experience poorer survival relative to Caucasian patients with Ewing sarcoma, synovial sarcoma, leiomyosarcoma, and some other soft-tissue sarcomas, but improved survival for rhabdomyosarcoma. While some of these tumors are largely driven by canonical translocation events (EWS-FLI1 in Ewing, SSX-SYT in synovial sarcoma), other soft tissue sarcomas are influenced by a number of sporadic genetic mutations. Further research is needed to expose whether racial disparities in sarcoma outcomes are dependent or independent of the underlying genetic drivers for various sarcoma sub-types.

5-year survival of sarcoma patients by race. Kaplan-Meier analsysis was used to compare survival according to race for all patients with sarcomas of soft-tissue or bone. The 5-year survival rates were 65% for Asian and 59% for African-American, compared with 63% for Caucasian (log-rank p-values for overall survival compared to White race were p=0.0590 and p<0.0001, respectively).



Independent predictors of mortality in sarcoma. Patient, demographic, tumor, and treatment variables were included in a proportional hazards analysis to assess for influence on overall survival. In addition to controlling for the confounding effects of other variables on survival, an interaction term (Race*Histology) was included to specifically determine the effect of race on survival within different tumor types.

Patient Demographic Variables		HR (95% CI)	P-Value
Age above median		1.82 (1.77-1.88)	<0.001 ***
Female sex		0.91 (0.89-0.94)	<0.001 ***
Race (Black vs. White)	STS, Other	1.14 (1.04-1.25)	0.006 **
	Fibrosarcoma	1.01 (0.90-1.13)	0.902
	Liposarcoma	1.03 (0.91-1.17)	0.616
	Leiomyosarcoma	1.13 (1.02-1.24)	0.021 *
	Rhabdomyosarcoma	0.81 (0.70-0.95)	0.008 **
	Synovial Sarcoma	1.21 (1.03-1.42)	0.024 *
	Osteosarcoma	0.98 (0.88-1.09)	0.700
	Chondrosarcoma	0.88 (0.73-1.06)	0.177
	Ewing Sarcoma	1.41 (1.09-1.82)	0.008 **
Comorbidity Score (vs. 0)	1	1.29 (1.24-1.34)	<0.001 ***
	≥2	1.87 (1.76-1.99)	<0.001 ***
Income below median		1.07 (1.04-1.10)	<0.001 ***
Insurance (vs. Private)	None	1.32 (1.23-1.41)	<0.001 ***
	Govt.	1.41 (1.37-1.46)	<0.001 ***
Academic facility type		0.85 (0.82-0.89)	<0.001 ***
Tumor and Treatment Variables			
Tumor size >5 cm		1.74 (1.67-1.81)	<0.001 ***
Grade (vs. Low)	Intermed.	1.79 (1.67-1.92)	<0.001 ***
	High	2.96 (2.79-3.15)	<0.001 ***
Metastases		2.82 (2.71-2.92)	<0.001 ***
Surgery		0.43 (0.41-0.44)	<0.001 ***
Positive Margins (vs. Negative)		1.44 (1.39-1.50)	<0.001 ***



Poster #269 3465948

CHARACTERISTICS AND LONG-TERM OUTCOMES OF SURGICALLY MANAGED HIGH-GRADE EXTREMITY CHONDROSARCOMA

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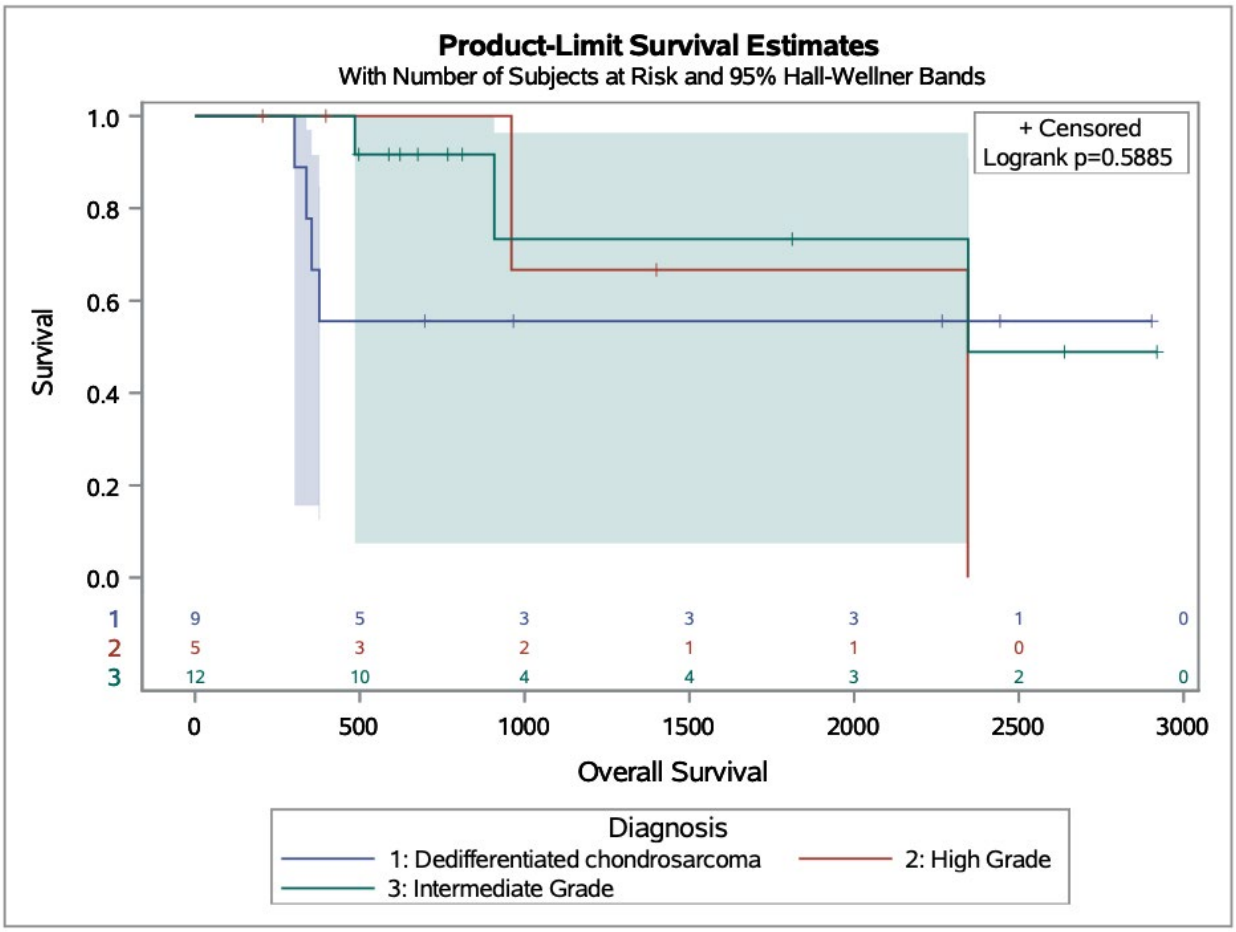
Objective: Chondrosarcoma is the third most common primary malignancy of the bone. Although rare, Dedifferentiated chondrosarcoma (DCS) is highly malignant that portends a poor prognosis. with approximately 22% of patients presenting with metastatic disease. Treatment of DCS includes surgical excision with wide margins; DCS tends to be resistant to both chemotherapy and radiation. Although factors such as clinicopathological characteristics, surgical margin, and adjuvant modalities likely play a role in overall survival, debate continues on the importance of these indicators. The purpose of this study is to further delineate the characteristics and long-term outcomes, local recurrence (LR) and survival, of patients with intermediate, high and dedifferentiated chondrosarcoma of the extremity at one tertiary institution.

Methods: Twenty-six cases of high-grade (conventional FNCLCC grades 2 and 3, dedifferentiated) chondrosarcoma were identified from an ongoing prospective cohort of 630 sarcoma patients managed surgically at a tertiary, university hospital between 9/1/2010-12/31/2019. A retrospective review of all pathology confirmed CS cases was performed. Cases were stratified into three groups based on tumor grade, including intermediate grade (IGCS), high grade (HGCS), and dedifferentiated chondrosarcoma (DCS). Patient demographics, tumor characteristics, surgical procedure, treatment course (radiation/chemotherapy), and survival data were collected and analyzed to determine prognostic factors for survival.

Results: In this cohort, there were 12/26 (46.2%) IGCS, 5/26 (19.2%) HGCS, and 9/26 (34.6%) DCS, with no difference patient demographics or comorbidities. DCS had a higher AJCC 7th/8th edition stage at diagnosis (0% IGCS, 20% HGCS, 33% DCS; p=0.04). Limb salvage was the most common primary procedure in every group (11/12 IGCS (91.7%), 5/5 HGCS (100%), and 7/9 DCS (77.8%); p=0.56). Pathology demonstrated margins included 8/12 (66.7%) wide (R0, >1mm) and 3/12 (25%) intralesional (R1/R2) for IGCS. For HGCS, there were 3/5 (60%) wide, 1/5 (20%) marginal, and 1/5 (20%) intralesional. A majority of DCS margins were wide, 8/9 (88.9%) with only 1 (11.1%) marginal. While there was no difference with surgical margin between the groups (p=0.85), there was a difference between the pathology measured surgical margin with the HGCS having the smallest margin of resection (IGCS: 0.125cm (0.1-0.35); HGCS: 0cm (0-0.1); DCS: 0.2cm (0.1-0.5); p=0.03). LR occurred in 5/9 (55.6%) DCS, 1/5 (20%) HGCS, and 1/14 (8.3%) IGCS patients. Fourteen total patients (53.8%) received systemic therapy, in which 3/14 (21.4%) developed LR versus 4/12 (33.3%) who did not receive systemic therapy (Table 1). Seven total patients (26.9%) received radiation therapy, while 3/7 (42.9%) developed LR. Overall systemic therapy and radiation did not impact incidence of LR (p=67; p=0.34).
The overall median follow-up was 26.0 months (IQR: 16.1-70.8). The time interval from resection to death was significantly lower in DCS (11.5 months (10.7-12.2)), followed by IGCS (30.3 months (16.2-78.2)), and HGCS (55.08 months (32-78.17)) (p=0.047). Additionally, death within 1 year was associated with the incidence of LR after resection (p=0.047 (OR: 13.5 95%CI: 1.1-166.0) (Figure 2). There was no correlation with the utilization of systemic therapy, radiation therapy, or margin and overall survival (p=0.63, p=0.52, p=0.74; Table 1). Surgical margin was not associated with the incidence of LR (p=0.32).

Conclusion: High-grade chondrosarcoma remains a fatal disease in many patients, particularly if associated with dedifferentiated subtype. Interestingly, all (100%) DCS patients who did not receive systemic therapy had LR. However, chemotherapy and radiation don't increase survival. In this case series, while HGCS had the smallest surgical margin, it had the longest time interval for both LR and death. Earlier identification of this rare disease may help in developing better management options.

Adjuvant Therapy per Grade			
Subtype	**Number**	**Local recurrence**	**Death within 1 year**
Intermediate-grade	**12**	**1**	**0**
Systemic Therapy	4	0	0
No Systemic Therapy	8	1	0
Radiation Therapy	1	0	0
No Radiation Therapy	11	1	0
High-grade	**5**	**1**	**0**
Systemic Therapy	4	1	0
No Systemic Therapy	1	0	0
Radiation Therapy	2	0	0
No Radiation Therapy	3	1	0
Dedifferentiated	**9**	**5**	**3**
Systemic Therapy	6	2	1
No Systemic Therapy	3	3	2
Radiation Therapy	4	3	2
No Radiation Therapy	5	2	1



Poster #270 3465964

IMPACT OF CHEMOTHERAPY TREATMENT ON OVERALL SURVIVAL IN DEDIFFERENTIATED CHONDROSARCOMA: AN ANALYSIS OF THE SEER DATABASE

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Objective: Dedifferentiated chondrosarcoma (DC) is a rare subtype of chondrosarcoma associated with poor prognosis and high rates of recurrence. A number of workers have proposed treatment of DC using osteosarcoma (OST) protocols, including the use of peri-operative chemotherapy. We used the Surveillance, Epidemiology, and End Results program (SEER) database to evaluate the impact of chemotherapy treatment on overall survival (OS) in primary DC treatment. A parallel analysis of OST was conducted as a control analysis.

Methods: We queried the SEER 1973-2016 database for DC and OST cases. The study population included cases that were diagnosed after year 2000 with locoregional disease of the bones and joints that had cancer-direct surgery performed. A total of 185 DC and 2261 OST cases were included. Baseline characteristics were compared using Fisher's exact or t-tests. Kaplan-Meier analyses and Cox proportional hazard models assessed the impact of clinical, demographic and treatment characteristics on overall survival (OS). Multiple Imputation (MI) was used to address missing data in multi-variable Cox models.

Results: DC patients were significantly older (median/me 66y range/r 18-95 DC, vs. me 17y r 3-91 OST, p<0.001) and more likely to be white race (94% DC vs. 75% OST, p<0.001) than OST patients. The remaining characteristics were similar in the two populations. Versus OST patients, those with DC were more likely to receive radiation therapy (RT; 20% DC vs. 4% OST, p<0.001) and less likely to receive chemotherapy (32% DC vs. 89% OST, p<0.001). OS at 3y among DC patients with localized or regional disease was similar (36%, 95% CI: 25% -48%, and 34%, 95% CI: 25%-42%, respectively). OS for OST at 3y with localized disease or regional disease was superior (84%, 95% CI: 81%-86%, and 72%, 95% CI: 69%-74%, respectively) (Table 1). In univariable Cox analyses, only age was statistically associated with OS among DC patients. In contrast, sex, age, tumor size, stage, tumor grade, primary tumor location, radiation and chemotherapy were all statistically associated with OS in OST. In an adjusted model for OST, all factors identified in the univariable analyses remained statistically significant, including receipt of chemotherapy (Hazard Ratio/HR: 0.61, 95% CI: 0.48-0.77, p<0.001) (Table 2). Only age was statistically significant in the multivariable model of OS in DC incorporating the same variables, including chemotherapy treatment (HR: 0.73, 95% CI 0.49-1.11, p=0.152).

Conclusion: Use of chemotherapy in primary DC is not associated with improved OS in those with local or regional disease receiving cancer-directed surgery. An identical analysis using OST cases, conducted as a positive control, demonstrated the known association of chemotherapy treatment with improved OS in OST. These results must be viewed cautiously, given the limited granularity of chemotherapy treatment information and concerns regarding chemotherapy misclassification in SEER data. Nevertheless, these data fail to support a strategy for primary treatment of DC employing chemotherapy protocols based on OST treatment.

Table 1. Overall survival by stage, % (95% Confidence Interval)

Stage	3 months	6 months	12 months	36 months
Dedifferentiated Chondrosarcoma				
Local	97 (89-99)	84 (73-91)	61 (48-72)	36 (25-48)
Regional	90 (83-94)	79 (71-86)	60 (51-69)	34 (25-42)
Osteosarcoma				
Local	100 (99-100)	99 (98-99)	96 (95-97)	84 (81-86)
Regional	99 (98-99)	98 (96-98)	93 (91-94)	72 (69-74)

Table 2. Cox multivariable analysis of overall survival

Variable	Dedifferentiated Chondrosarcoma	Osteosarcoma
	n=185	n=2261
	Hazard Ratio (95% CI), p-value	Hazard Ratio (95% CI), p-value
SEX		
Male	Reference Group	Reference Group
Female	0.76 (0.53-1.10), 0.142	0.82 (0.71-0.96), 0.012
AGE$		
<=66	Reference Group	
>66	1.52 (1.06-2.19), 0.024	
<=17		Reference Group
>17		1.65 (1.41-1.93), <0.001
SIZE*		
<=8 cm	Reference Group	Reference Group
>8 cm	1.25 (0.85-1.84), 0.260	1.24 (1.03-1.48), 0.020
STAGE		
Local	Reference Group	Reference Group
Regional	1.04 (0.71-1.53), 0.825	1.61 (1.37-1.90), <0.001
HISTOLOGIC GRADE*		
Low (Grade I and II)	Reference Group	Reference Group
High (Grade III and IV)	1.25 (0.69-2.27), 0.457	2.95 (1.93-4.51), <0.001
PRIMARY TUMOR LOCATION		
Extremities	Reference Group	Reference Group
Trunk, skull, bone NOS	0.67 (0.36-1.24), 0.201	1.78 (1.33-2.38), <0.001
RADIATION THERAPY		
No/unknown	Reference Group	Reference Group
Yes	1.23 (0.78-1.92), 0.372	1.91 (1.44-2.53), <0.001
CHEMOTHERAPY		
No/unknown	Reference Group	Reference Group
Yes	0.76 (0.50-1.14), 0.184	0.61 (0.47-0.77), <0.001

*Multiple imputation was used to address missing data for primary tumor size and histologic grade.

$ For age, the data were dichotomized into two groups based on the median age in each analysis.

Poster #271 3466167

A RARE CASE SERIES OF COMPOSITE HEMANGIOENDOTHELIOMA PRESENTING AS BONE TUMOR

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Objective: Composite hemangioendothelioma(CHE) is a rare neoplastic disorder of vascular origin. It has never been reported as a bone tumor presentation of lower extremities. We wanted to share this first reported presentation, not in one but in two of our patients presenting as a locally aggressive tumor of bones of the lower extremities.

Methods: A 36-year-old Caucasian male presented with a one-month history of pain in his left foot. X-ray of the foot showed a non-displaced fracture and the patient was prescribed a boot. A two-week follow up x-ray showed multiple lytic areas, prompting bone scan (shown Figure 1). MRI of the left foot and ankle showed innumerable T1 hypointense and T2 hyperintense enhancing masses throughout bones of the ankle and foot, with the largest measuring 4 cm. Biopsy of the foot bone shown. (Top four slides). Immunohistochemical stains were consistent with CHE. Patient underwent left below-knee amputation. Patient was prescribed propranolol with benefit showed in angiosarcoma studies. He is currently three years out from his initial surgery.

A 22-year-old Caucasian male presented with a two-week history of pain in his left foot and subsequent knee pain. MRI showed multiple T1 hypointense and T2 heterogeneously hyperintense lesions involving the tibia, patella, femur and bones of the foot, measuring upto 5 cm. Bone scan shown. (Figure 2). Biopsy of the left calcaneus mass lesion and tibial lesion shown (Bottom four slides). Immunohistochemical studies were consisitent with CHE. Patient underwent above-knee amputation. The patient continues to follow-up with surveillance imaging.

Results: CHE has previously been reported in various soft tissue locations and internal organs. But presentation in the bones is extremely rare with only one previous case report of CHE presenting in the manubrium sternii. CHE can occur at any age and is more common in females than males (3:2 ratio). Bone CHE presents in both cortical and medullary spaces in multiple locations. Histopathologically, CHE exhibits admixture of histologically distinct components of benign and malignant vascular components which vary greatly in their relative proportions. CHE contains areas that resemble at least two of the following tumors: spindle cell hemangioma, epithelioid hemangioendothelioma, retiform hemangioendothelioma, Kaposiform hemangioendothelioma, papillary intralymphatic angioendothelioma or angiosarcoma-like areas. CHE tumors are positive for endothelial markers CD31 and CD34 by immunohistochemistry. ERG (ETS-related gene) is a highly specific marker for benign and malignant tumors of endothelial origin and is expressed by composite hemangioendothelioma.

CHE is a locally aggressive and rarely metastasizing tumor. Surgical excision beyond the clinical margins is usually the treatment of choice given the high propensity for local recurrence. There is one reported case of cutaneous CHE treated with interferon-alpha 2b with partial recovery. One patient with nasal CHE was treated with electron beam therapy with reported improvement. Synergistic activity of propranolol and vinblastine-based metronomic chemotherapy has been observed in advanced angiosarcoma with 100% response rate with one complete response. The rationale for this combination therapy was based on previous work on non-specific beta blocker, propranolol in treating infantile hemangioma and in vitro anti-proliferative effects of propranolol against endothelial cells. Whether all patients with aggressive hemangioendothelioma should be considered for nonselective beta-blocker therapy is unclear at this time.

Conclusion: CHE is a rare disease and treatment strategies are not well defined. Our cases demonstrate bone in lower extremities as being a primary location for CHE. This differential should be considered especially in younger patients having persistent bone pain. Surgical excision appears to be a successful modality. More information is needed to delineate other treatment options.

Fig 1: Multiple foci of abnormal uptake in left distal tibia, hindfoot, and mid- and forefoot.

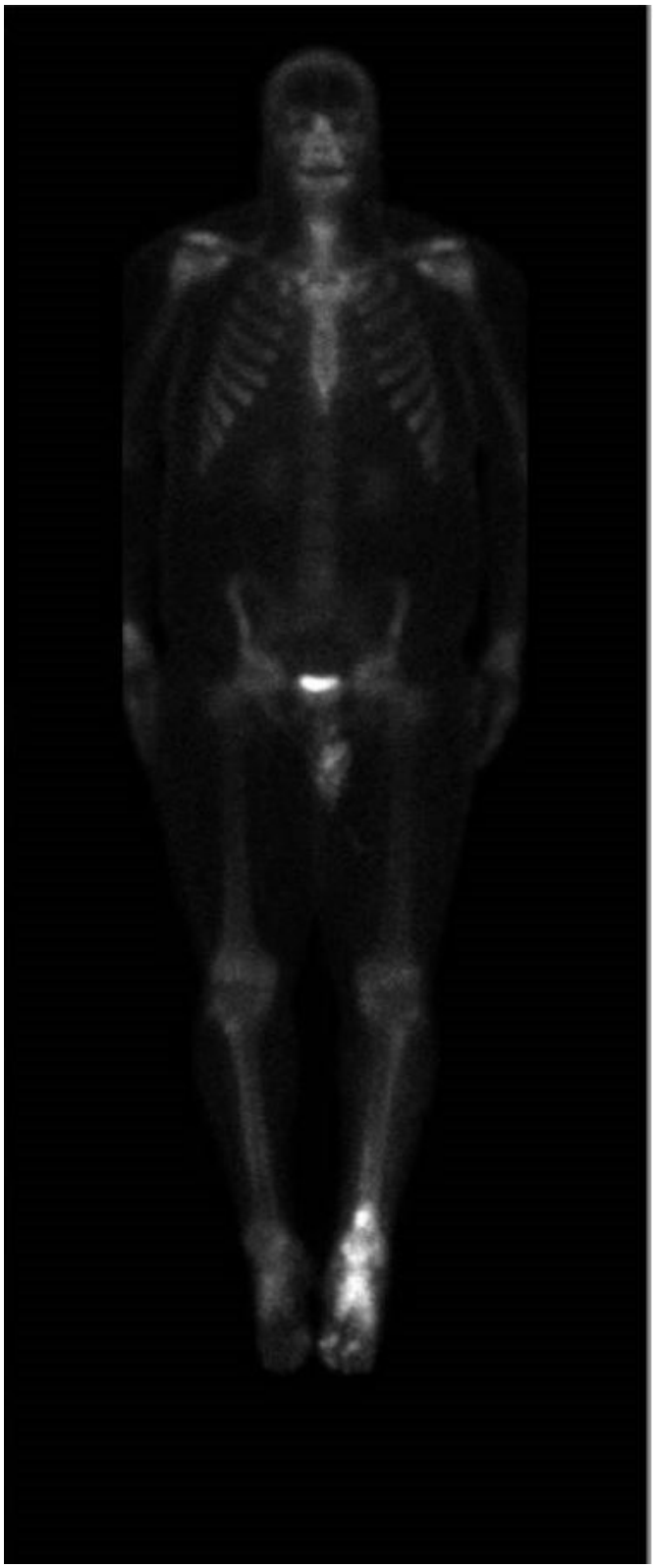
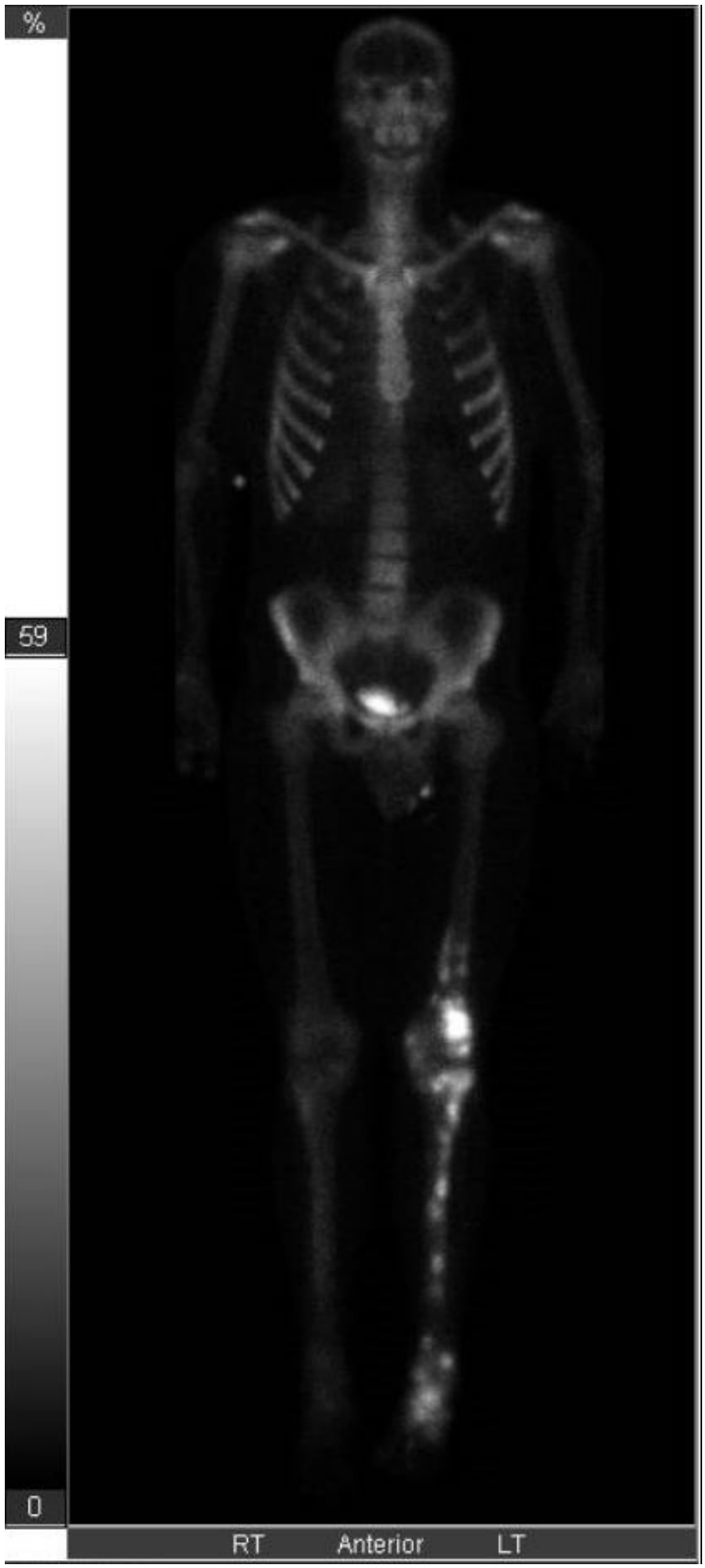
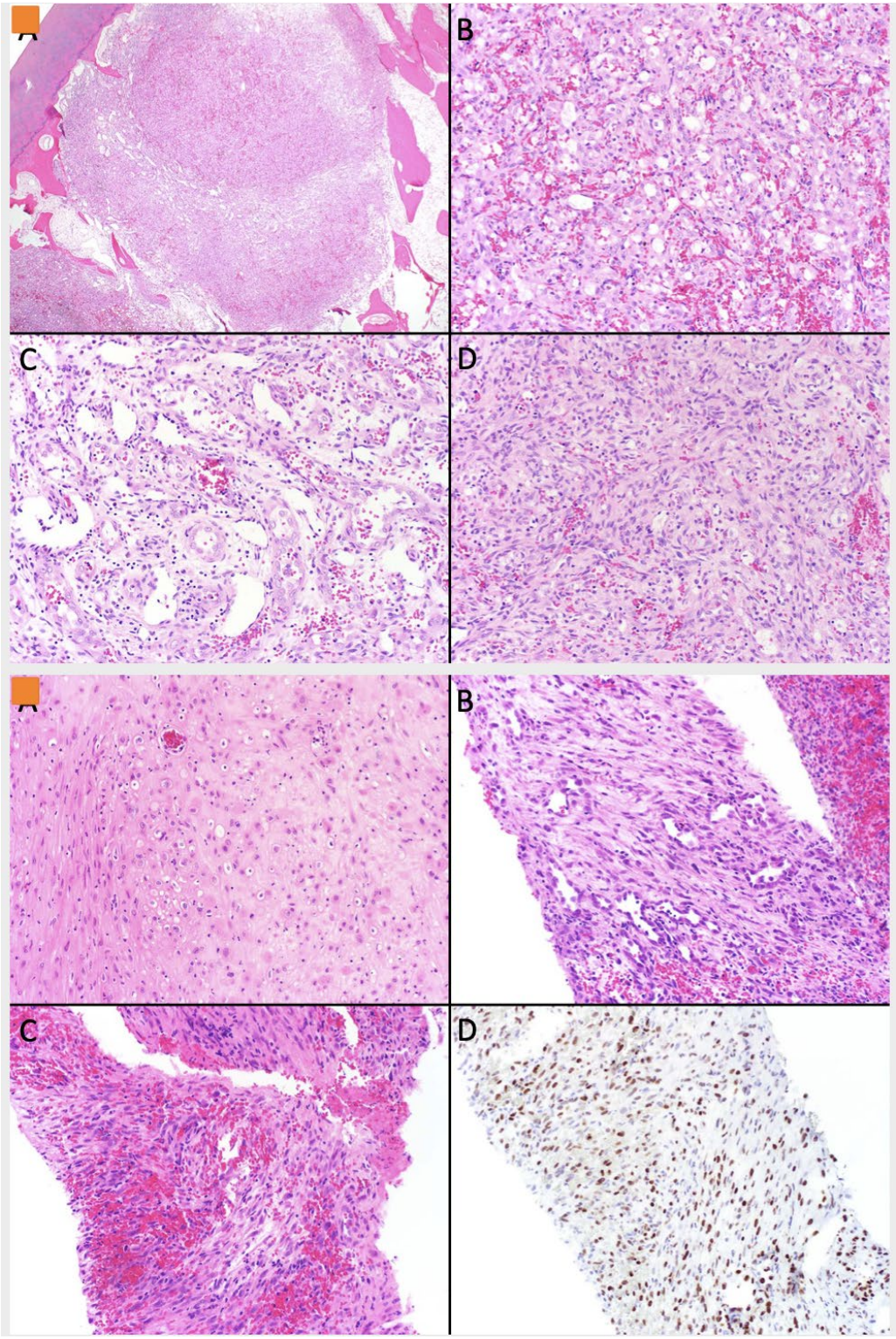


Fig 2: Scattered avid radiotracer foci in the distal left femur, left patella, entire left tibia, left calcaneus, and left metatarsals.



Top four slides: A. This large, multinodular tumor demonstrates varying histologies, including B. areas composed of anastomosing cords of epithelioid cells with prominent cytoplasmic vacuolization, C. those with well-defined vascular lumina lined by flat or plump endothelium, and D. those composed of haphazardly arranged bland spindle cells (H&E, 20x for A, while all others are 200x)

Bottom four slides: A. The majority of this patient's multiple tumors resembled epithelioid hemangioendothelioma (EHE), composed of vacuolated epithelioid cells arranged singly and in cords, set in myxohyaline stroma. B. In other areas, well-defined vascular lumina lined by plump endothelium and C. cellular spindle cell areas were present. D. ERG was expressed throughout, including in the cellular spindle cell areas, confirming the tumor's vascular nature. Neither CAMTA1 or TFE3 fusion was detected in either of these two cases, excluding EHE.



Poster #272 3467206

COMPREHENSIVE COMPLICATION INDEX BETTER ESTIMATES THE IMPACT OF COMPLICATIONS IN RETROPERITONEAL SARCOMA SURGERY COMPARED TO CLAVIEN-DINDO CLASSIFICATION

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Objective: Surgery for primary retroperitoneal sarcomas (RPS) often requires a technically demanding, en bloc multivisceral resection to optimize outcomes. Clavien-Dindo Classification (CDC) is a validated method to report complications in different types of surgery. Comprehensive complication index (CCI) is a more recent system to report complications, based on a linear ranging scale. Differently from CDC, it considers the overall burden of complications. CCI has been already validated in abdominal surgery. However, no studies investigated yet its validity in surgery for RPS. The aim of our study is to compare CDC and CCI in describing the impact of complications after surgery for RPS on postoperative length of stay (PLOS).

Methods: A total of 325 patients were identified. For each patient, data on subsequent surgeries for RPS recurrences were also recorded. In conclusion 422 different surgeries were retrospectively analyzed between March 1997 and October 2019. Patient demographics, pathology, complications and their treatments, and PLOS were reviewed. The organs resected were classified using a weighted resected organ score intended to provide a more accurate and standard representation of anticipated morbidity than simply reporting the number of organs resected. The CCI was calculated for each patient. Linear regression was used to assess whether the CCI and CDC correlate to PLOS.

Results: The 422 procedures were reviewed, in 84 (19.7%) just the tumor was resected, in 87 (20%) just one organ was resected, in 73 (17.3%) two organs were resected, in 178 (42.2%) multivisceral resection was performed. The median number of resected organs was 2 (IQR 1-4). Median diameter was 100mm (IQR: 70-180mm), while more frequent histologic subtypes were: well-differentiated liposarcoma in 80 procedures (24.6%), dedifferentiated liposarcoma in 76 (23.4%) and leiomyosarcoma in 63 (19.4%). In 170/422 procedures (40%) postoperative complications occurred; 106 (25.1%) had just one complication while 64 (15.2%) had multiple complications. Reoperation due to postoperative complications was performed in 56 patients (13.3%). Among the procedure the 5.9 % presented a grade I complication according to CDC; 16.4% grade II, 5% grade IIIa, 33% grade IIIb, 3.8% grade IVa and 0.2% grade IVb, 1.2% grade V (death). Considering the 170 surgeries that had complications, the mean CCI was 30 (range 8.7-100), the median was 22.6 (IQR 20.9-34.8). Severe postoperative adverse events (classified as CDC ≥ 3) occurred in 76/422 (18%) surgeries. Mean PLOS was 14.6 days with a range from 0 to 148, while median was 8 days (IQR 7-15). Univariable linear regression selected age, comorbidities, duration of surgery, tumour presentation, tumour size, multivisceral resections, numbers of resected organs, complications, CDC grade, severe postoperative events (CDC≥3), CCI grade, reoperation and ICU admission as predictive factors for PLOS. Two different multivariable linear regressions were applied, the model with CDC selected number of resected organs, multivisceral resection, length of ICU stay and CDC as independent prognostic factors for PLOS ($p<0.001$); the model with CCI selected number of resected organs, multivisceral resection, length of ICU stay and CCI as independent prognostic factor for PLOS ($p<0.001$). The AIC and BIC for the CCI model were smaller (3089.687 and 3137.764, respectively) than for CDC (3093.481 and 3141.557, respectively), suggesting CCI to fit better than CDC. Finally, a higher correlation index for CCI and PLOS ($r = 0.6921$) compared to CDC and PLOS ($r = 0.6879$) was appreciated.

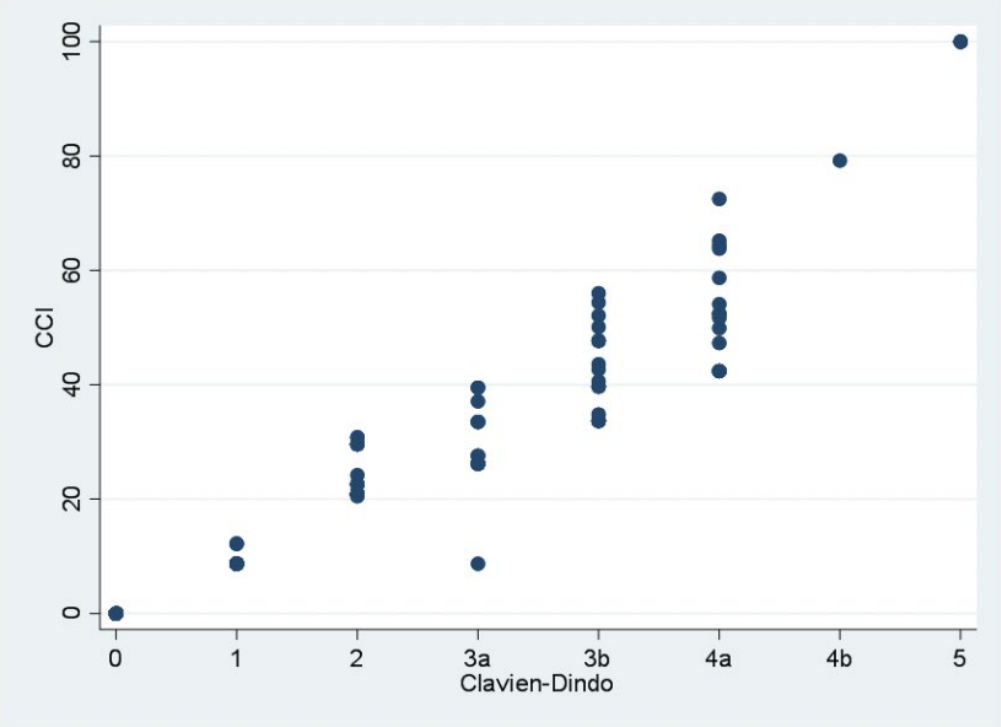
Conclusion: The Comprehensive Complication Index was found to be a valid method to capture and classify the overall burden of complications after RPS surgery and their impact on PLOS of patients. Moreover, it describes the real impact of complications better than CDC.

Univariable linear regression analysis

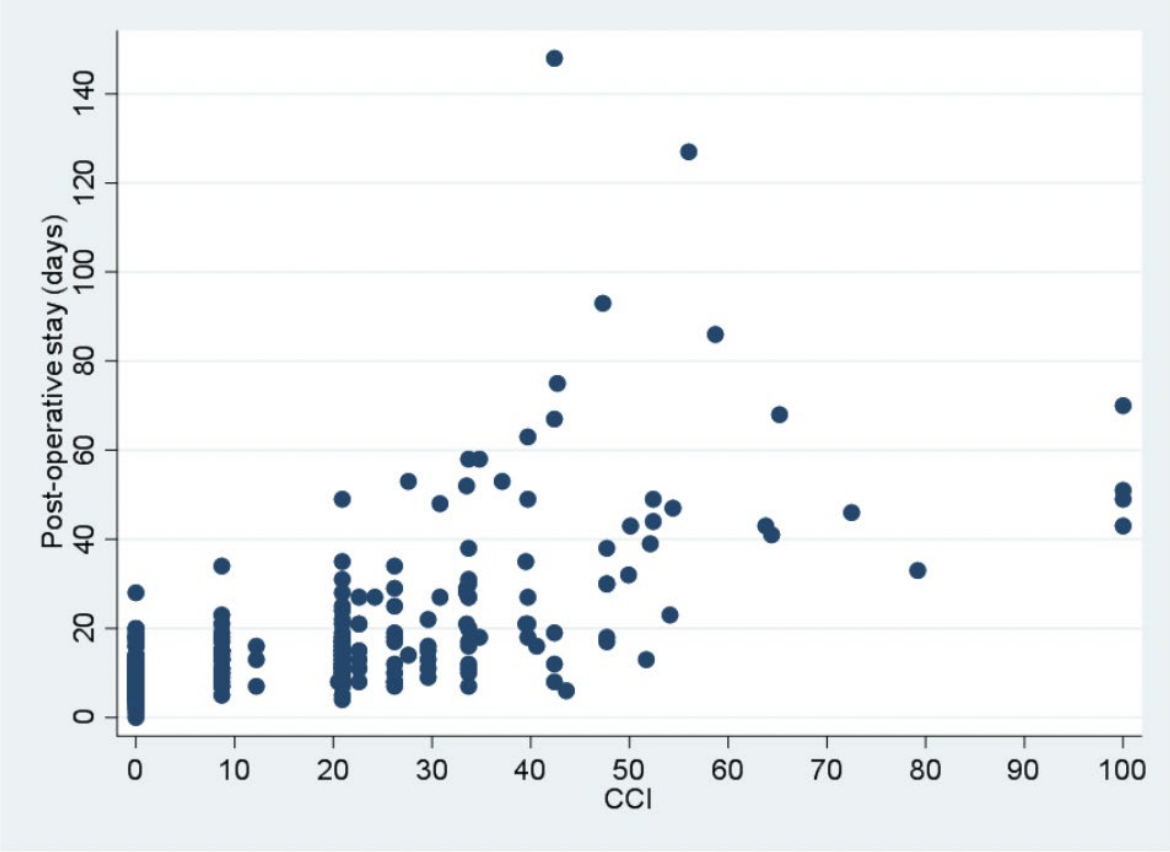
Variable	Coeff. (95% CI)	p Value
Sex	-2.75 (-5.73-0.21)	ns
Age	0.15 (0.05-0.25)	0.003
Metastasis	-2.28 (-7.18-2.62)	ns
Comorbidities	3.61 (0.65-6.5)	0.017
Duration of surgery	0.04 (0.03-0.06)	<0.001
Multifocality	-1.04 (-4.74-2.66)	ns
Tumour presentation	-2.4 (-3.88- -0.93)	0.001
Tumour size	0.05 (0.04-0.06)	<0.001
Tumour grade	0.01 (-2.48-2.50)	ns
Completeness of resection (R0/1/2)	3.19 (-0.89-7.28)	ns
Multivisceral resection	5.75 (2.76-8.74)	<0.001
Nr of resected organs	2.43 (1.83-3.02)	<0.001
Patterns of resection	----------	----------
No organs resected or organs weighted 0	-4.98 (-8.47- -1.5)	0.005
Other	-4.38 (-7.34-1.42)	0.004
Colon, Kidney +/- other	10.29(5.85-14.74)	<0.001
Colon, Kidney, Spleen, Pancreas +/- other	13.59 (6.36-20.81)	<0.001
Vascular resection +/- other	5.43 (-0.50-11-37)	ns
Pancreaticoduodenectomy +/- other	-0.60 (-31.13-29.9)	ns
Postoperative complications	15.68 (13.04-18.31)	<0.001
CDC≥3	24.91 (21.86-27.97)	<0.001
CDC	6.35 (5.68-7.03)	<0.001
CCI	0.57 (0.51-0.63)	<0.001
Reoperation for complications	27.63 (24.11-31.14)	<0.001
ICU admission	25.85 (21.84-29.86)	<0.001

Multivariate analysis of PLOS for the model that include CCI

Variable	Coeff. (95%CI)	p Value
Sex	0.15 (-1.97-2.27)	0.887
Age	0.04 (-0.04-0.13)	0.321
Comorbidity	-0.37 (-2.94-2.02)	0.777
Tumur origin	0.52 (-0.60-1.64)	0.361
Tumour size	0.01 (0.01-0.02)	0.015
Duration of surgery	0.01 (-0.01-0.01)	0.259
Multivisceral resection	-5.96 (-9.19 to -1.74)	<0.001
Number or resected organs	1.80 (1.05 to 2.56)	<0.001
CCI	0.44 (0.36-0.52)	<0.001
ICU admission	8.89 (4.67 to 13.1)	<0.001



Scatterplot of the distribution of CCI according to CDC



Scatterplot of the distribution of PLOS according to CCI

Poster #273 3467207

FOCUSED ULTRASOUND FOR APPENDICULAR SOFT-TISSUE SARCOMAS: TARGETABILITY ASSESSMENT FOR TISSUE-SELECTIVE TREATMENTS

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Objective: Focused ultrasound has been investigated as a noninvasive, nonionizing, repeatable treatment for appendicular soft tissue sarcomas (STSs), and standardized targetability criteria are needed to guide future clinical trials. Promising focused ultrasound modalities for STSs include high-intensity focused ultrasound (HIFU) and histotripsy. HIFU is typically MR-guided and uses an extracorporeal transducer to focus continuous, high-intensity ultrasound in a controlled manner, inducing thermal necrosis in an internal focal region while sparing intervening tissues. Histotripsy treatment is also delivered via an extracorporeal transducer but is ultrasound-guided and uses short pulses of high-intensity ultrasound to produce primarily mechanical tissue ablation. Recent feasibility studies in animal models have demonstrated the possibility of designing histotripsy treatments that are tissue-selective (e.g. spare healthy tissue and neurovasculature) based on differences in the mechanical properties of tumors and surrounding tissue. Previous feasibility studies of focused ultrasound treatments for solid tumors have failed to account for three-dimensional anatomy and potential tissue-selective effects. This study aims to develop a three-dimensional focused ultrasound targetability assessment for STSs that includes consideration of tissue-selectivity.

Methods: A subset of appendicular STS patients from the Michigan Medicine Sarcoma Archive with sufficient pretreatment imaging is identified. Materialise Mimics software is then used to construct three-dimensional renderings of tumors and significant surrounding nerves and blood vessels. An acoustic window analysis assuming a spherical transducer design is used to assess tumor targetability and potential for collateral damage during ablation.

Results: The three-dimensional feasibility assessment finds that a majority of appendicular STSs are targetable with focused ultrasound. The assessment also identifies a subset of STSs that would not be safely accessible to HIFU but could potentially be treated using tissue-selective histotripsy.

Conclusion: Our methods are general and account for three-dimensional anatomical detail, thus permitting more accurate focused ultrasound targetability assessments for STSs and other solid tumors. The risk of thermal spread is shown to limit the applicability of HIFU and illustrates the potential utility of histotripsy for tumors located near significant neurovascular structures.

Poster #274 3467256

FOSB-ACTB FUSION IN PSEUDOMYOGENIC HEMANGIOENDOTHELIOMA: CASE STUDY OF THE YOUNGEST PEDIATRIC PATIENT.

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Objective: Pseudomyogenic Hemangioendothelioma (PHE) is a rare vascular tumor with intermediate malignancy potential which affects soft tissues and bones. PHE lacks morphologic features of vascular differentiation and can only be identified through relevant immunohistochemical stains such as the MSK-IMPACT assay and archer assay. There have been 129 reported cases since it was first described in 2003 as an epithelioid-sarcoma-like hemangioendothelioma. (Raptopulous et al, 2018). Since then, a balanced t(7;19)(q22;q13) translocation resulting in the fusion of the Finkel-Biskis-Jinkins murine osteosarcoma viral oncogene homolog B/Serpin Family E Member 1, FOSB-SERPINE1 gene fusion has been found in the majority of cases. SERPINE1 normally functions as a fibrinolysis inhibitor through the inhibition of tissue plasminogen activator (tPA) and urokinase (uPA). However, a minority of cases of PHE have been described with different partner genes (ACTB gene) to FOSB. The ACTB gene encodes actin proteins that are necessary for cell structure, mortality, intercellular signaling, and integrity. Knowledge of the atypical PHE cases, involving a different partner gene for FOSB, is important to direct appropriate treatment. We describe the youngest known case of PHE of the bone who was found to have a rare FOSB fusion partner: ACTB (BETA-ACTIN ACTIN, CYTOPLASMIC). These lead to appropriate anti-VEGF treatment and prevent the child from having an amputation, the only therapy initially offered at presentation.

CASE STUDY

A 6-year-old boy presented with right ankle pain at football practice. He was initially diagnosed with an ankle sprain, until it worsened over several weeks prompting plain film imaging that revealed a lytic expansile bone lesion of the distal fibular metaphysis along with patchy sclerosis of multiple bones of the foot and proximal and distal tibial and fibular metaphysis. On referral to orthopedics, a biopsy was read as multifocal bony "infection versus PME"; Pathology showed "infiltrative clusters of large rounds to elongated cells with abundant homogeneously staining dense eosinophilic cytoplasm suggestive of muscle differentiation with characteristic FLI-1, CD31, and cytokeratin AE1/AE3 but Vascular channel formation" and "intracytoplasmic Lumina" were not seen. A repeat biopsy demonstrated sparse tumor cells with surrounding inflammatory infiltrate and loss of AE1/AE3 staining (Fig. 2) thought to be consistent with an initial response to treatment in the setting of an infectious/inflammatory. Next-generation sequencing of the first and second tumor biopsies failed to detect the (7;19)(q22;q13) FOSB/SERPINE1 fusion, thought to be characteristic of PHE. A third attempt, looking for circulating DNA in the blood, however, showed a FOSB gene fusion with previously undescribed partner gene: ACTB (BETA-ACTIN ACTIN, CYTOPLASMIC) interpreted as confirming the histologic diagnosis of PME. This confirmation steered the team to successful treatment with sirolimus, zoledronic acid, and pazopanib, instead of radical, ablative surgery.

Methods: The literature search was performed using Google Scholar and PubMed with terms: "Pseudomyogenic hemangioendothelioma," "FOSB gene", "ACTB gene", "epithelioid sarcoma-like hemangioendothelioma" selected for patients under 30 and English language.

Results: Upon completion of the literature review, it is apparent that this patient is the youngest patient to be affected by PHE with FOSB/ACTB gene fusion. Among the reviewed cases, most of the clinical presentations of PHE involving the FOSB/ACTB gene fusion were multifocal and mostly affected the bone.

Conclusion: Fortunately, the treatment option that was used for this patient prevented an amputation and he has not relapsed in 6 years. Finally, if there is a vascular bone tumor whereby PHE is considered, it is important to look for multiple gene fusions. This practice has the potential of improving the treatment plan and the overall outcome of the treatment.

Age (y)/Sex	Site	Clinical Presentation	Depth
38/M	Abdominal Wall	Multifocal	Superficial — Dermis and Subcutaneous
24/M	Calf	Solitary	Deep — Soft Tissue
19/M	Toe and Tibia	Multifocal	Deep — Bone
25/M	Foot	Solitary	Deep — Bone
44/M	Humerus	Solitary	Deep — Bone
54/F	Shoulder	Solitary	Superficial — Dermis and Subcutaneous
45/F	Ankle	Multifocal	Deep — Bone
25/M	Cuboid bone	Multifocal	Dermis, Subcutaneous, and Skeletal muscle
69/M	Pancreas	Multifocal	Soft Tissue
54/F	Posterior Deltoid	Solitary	Dermis and Subcutaneous
15/M	T2 Vertebral	Multifocal	Soft Tissue
33/M	Sacral Bone and Lumbar Spine	Multifocal	Deep— Bone
17/M	Leg (Calf)	Multifocal	Soft Tissue — Epidermis and Subcutaneous

Table 1. Summary of PMH cases with FOSB/ACTB Gene Fusion Listed by Age, Sex, Site, Depth and Clinical Presentation.

Poster #275 3467312

THE AMERICAN COLLEGE OF SURGEONS (ACS) SURGICAL RISK CALCULATOR UNDERESTIMATES THE ACTUAL RISKS OF SURGERY FOR RETROPERITONEAL SARCOMA: RESULTS FROM A REFERRAL CENTER

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Objective: Surgery for retroperitoneal sarcomas (RPS) often requires a technically demanding, en bloc multivisceral resection. Nowadays, a validated risk calculator tailored to sarcoma surgery is not available to predict surgical short-term outcomes. The American College of Surgeons National Quality Improvement Program (ACS NSQIP) surgical risk calculator has been endorsed by the surgeons' community to counsel patients and relatives regarding estimated postoperative complications. To calculate the risks, it is mandatory to insert a Current Procedure Technology (CPT) code, which refers to a single specific surgical procedure, and patient characteristics. The aim of this study was to assess the ACS calculator's ability to predict complications, mortality and length of stay (LOS) in patients undergoing surgery for primary RPS at our referral center.

Methods: Data were analyzed retrospectively from our prospectively maintained database. Ninety-one patients who underwent surgery for primary RPS, between 2009 and 2018, at Humanitas Clinical and Research Center-IRCCS (Rozzano, Milan), were evaluated. Complications were graded based on Clavien-Dindo Classification (CDC). Complications graded CDC >= 3 were considered "serious". Predicted risk for outcomes was calculated in the on-line ACS calculator using the code indicative of most comorbid organ resection. Rates of complications, mortality and LOS determined by the ACS calculator were compared to the actual 30-day rates.

Results: Overall predicted rates of any morbidity (mean 36.3% vs. 12.3% ± 6.9; P<0.001), serious complications (mean 19.8% vs. 10.0% ± 5.6; P<0.001), mortality (mean 2.2% vs. 0.5% ± 1.1; P<0.001), and LOS (mean 17.9 days ± 19.4 vs. 4.3 days ± 1.7.; P<0.001), were significantly lower than actual rates. The predicted risk of each complication extracted from the ACS calculator (cardiac complications, surgical site infection, urinary tract infection, venous thromboembolism, and renal failure), was underestimated compared to the related actual rate (p<0.001). Additionally, the predicted risk of reoperation was underestimated (p<0.001). On the other hand, postoperative pneumonia and readmission after discharge appeared overestimated (p<0.001).

Conclusion: The ACS calculator underestimates the actual risks of surgery for retroperitoneal sarcoma giving an optimistic estimation of complication rates and LOS. Our results highlight the calculator's inability to insert more than one CPT code, limiting the effectiveness in multivisceral surgery. Future revisions of the risk calculator should consider the option to include more than one CPT code. The creation of a RPS specific risk calculator should be taken under consideration.

Poster #276 3467373

WHAT IS THE UTILITY OF CHEST SURVEILLANCE FOR ATYPICAL LIPOMATOUS TUMORS OF THE EXTREMITIES?

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Objective: Atypical lipomatous tumors (ALTs) are a commonly encountered tumor of the extremities. Accepted management includes marginal resection; the propensity for metastasis is considered to be very low. Because of the prior characterization of ALTs as "well-differentiated liposarcomas," many institutions continue to include chest imaging as part of planned surveillance. Despite this, a standard of care for surveillance, with regard to duration and need for imaging, has not been established. The purpose of this study was to investigate the utility of surveillance and chest imaging in ALTs.

Methods: This was a multi-institution, retrospective review of all patients from three tertiary care referral centers with primary ALTs of the back and extremities undergoing surgical resection from 2006 to 2019. We excluded all patients with thoracic, abdominal and retroperitonenal liposarcomas. Univariate and multivariate analyses were used to correlate specific outcome measures with survival. Long-term survival was evaluated using the Kaplan-Meier (KM) method.

Results: 285 patients with a diagnosis of ALT were included. The average age was 61.9 years with an average follow up of 33.9 months (1-180 months). The average BMI was 27.8. 133 (46.7%) patients had MDM2 positive tumors while 128 (44.9%) patients did not have MDM2 testing performed. The average tumor size was 17.8 cm (1.1-45.7 cm). 217 (76.1%) tumors were located in the buttocks or thigh, 24 (8.4%) in the arm or shoulder, 12 (4.2%) in the leg and 32 tumors located elsewhere. 167 (58.6%) patients had a marginal excision or grossly positive margins. Patients received an average of 0.7 CT scans and 1.1 chest radiographs over the surveillance period. Based on US average cost data, the average cost for imaging used for chest surveillance was $811.25. From 202 CT scans of the chest, the number of incidental findings prompting further intervention was 3 (1.5%) including one aortic aneurysm and two hiatal hernias.

There was a single presumed metastasis by CT that occurred after a patient had a local recurrence; the patient died from a heart attack and the lesion could not be biopsy proven. This tumor did not undergo MDM2 testing. The 10-year metastasis free survival was 99.6%. There were 41 patients (14.4%) with local recurrences or residual disease that progressed; 19 of these patients (46.3%) had MDM2 positivity, while 21 (51.2%) had no MDM2 testing completed. This resulted in a 10-year local recurrence free survival was 85.6%. A single local recurrence recurred as biopsy proven high grade liposarcoma; original pathology was MDM2+. No patients had a documented death from disease.

Conclusion: For ALTs, the utility of surveillance has not been well defined. Within this cohort, there was great variety in the duration and type of surveillance performed. This study suggests that advanced imaging does not have a significant role in the surveillance of primary ALTs. Advanced imaging may be considered in cases of local recurrence.

Poster #277 3467404

PREDICTING THE SURVIVAL PROBABILITY AND ASSESSING PROGNOSTIC FACTORS IN PATIENTS WITH MALIGNANT EPITHELIOID HEMANGIOENDOTHELIOMA OF BONE: A POPULATION-BASED ANALYSIS

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Objective: Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor with malignant potential. Though found in soft tissue, EHE may arise in bone, where its incidence is 1% of all primary bone neoplasms. Few cases have discussed the long-term survival of patients with osseous EHE at ranges between 33% and 92%. However, consensus survival estimates from large series are lacking due to disease rarity. This study sought to identify a large cohort of patients with osseous EHE to ascertain the demographics, prognostic factors, and survival of patients with this exceedingly rare sarcoma subtype.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database provisioned by the National Cancer Institute was queried from 1973 to 2016. Patients with microscopically confirmed, malignant osseous EHE were identified by Histologic International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes 9130/3. Outcome variables were patient demographics, tumor characteristics, treatment modalities, and disease specific survival (DSS) and overall survival (OS).

Results: Forty-six patients from 1975 to 2016 were identified. The mean age at diagnosis (years, range, Interquartile Range (IQR)) was 47.8 (2-91, 68-26) and 60.9% were female. 27 (58.7%) cases originated in the appendicular skeleton (small and long bones of limbs, scapulae), 18 (39.1%) in the axial skeleton (facial and skull bones, mandible, vertebrae, sternum/ribs, pelvis), and 1 (2.2%) were unspecified. 23.9% were Grade I (well-differentiated), 17.4% were Grade II (moderately differentiated), 6.5% were Grade III (poorly differentiated), 2.2% were Grade IV (undifferentiated), and 50% were unspecified. For cases after 2003 (e.g. those with recorded tumor characteristics), 1 (7.1%) had metastatic disease at diagnosis. For cases after 2003 with recorded tumor extension, 4 (28.6%) were localized to bone, 4 (28.6%) involved adjacent soft tissue or skeletal muscle, and 6 (42.8%) had unspecified extension. For cases after 2003 with recorded therapy, 5 (35.7%) had surgical intervention, 5 (35.7%) had no surgery, and therapy for 4 (28.6%) was unknown. Ten and 20-year DSS and OS estimates were 78% and 78%, and 80% and 72%, respectively (Figure 1). The mean (95% CI) disease-free survival (mos.) of patients with osseous EHE was 376.95 (311, 442), and for all-cause survival was 384.66 (312, 457). No covariables including Grade, primary site, tumor extension, therapy, age, or gender were found to be of significant prognostic influence for either DSS or OS.

Conclusion: Little remains known about osseous EHE. In its second largest identifiable study, 10 and 20-year DSS and OS of 46 patients with osseous EHE progress somewhat similarly, though with 10-year estimates below previously reported levels. Additionally, neither tumor characteristics nor demographics including primary site, age, or gender were found to be of prognostic significance in DSS or OS. These data may allow patients with this rare form of cancer to be better informed about their disease course, and they may educate sarcoma care providers on what to expect when confronted with a case of osseous EHE.

Figure 1. Disease-specific survival estimates for patients with malignant hemangioendothelioma of bone appears to show more pronounced short-term disease-specific mortality than all-cause mortality.

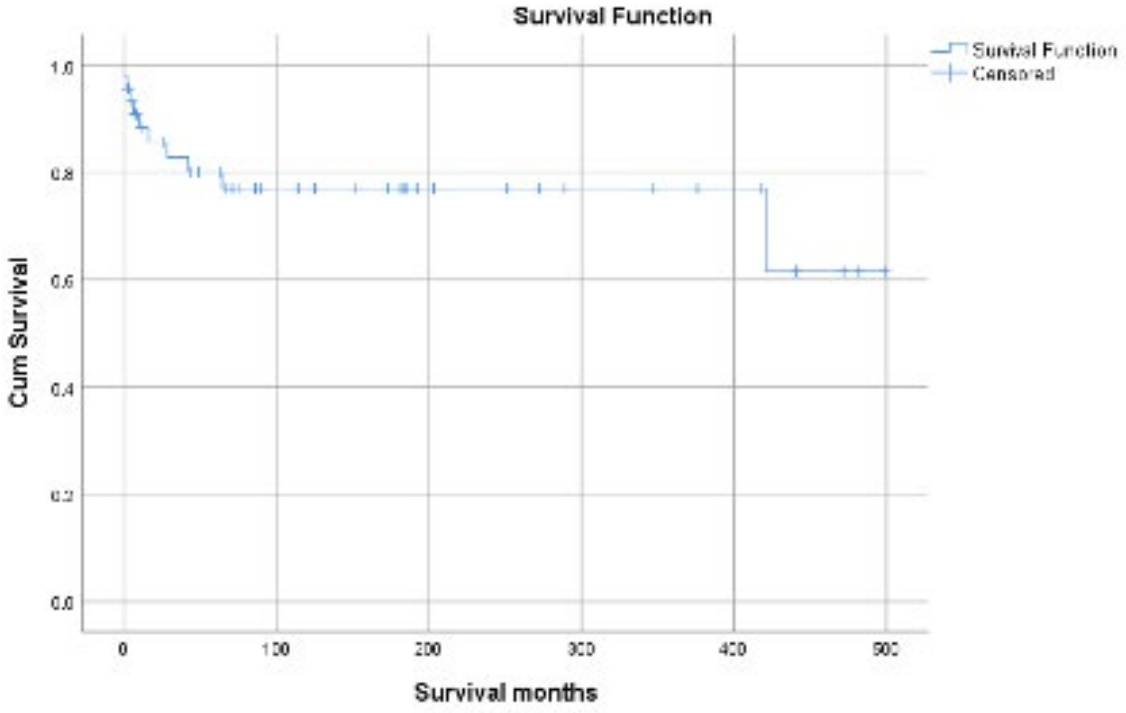
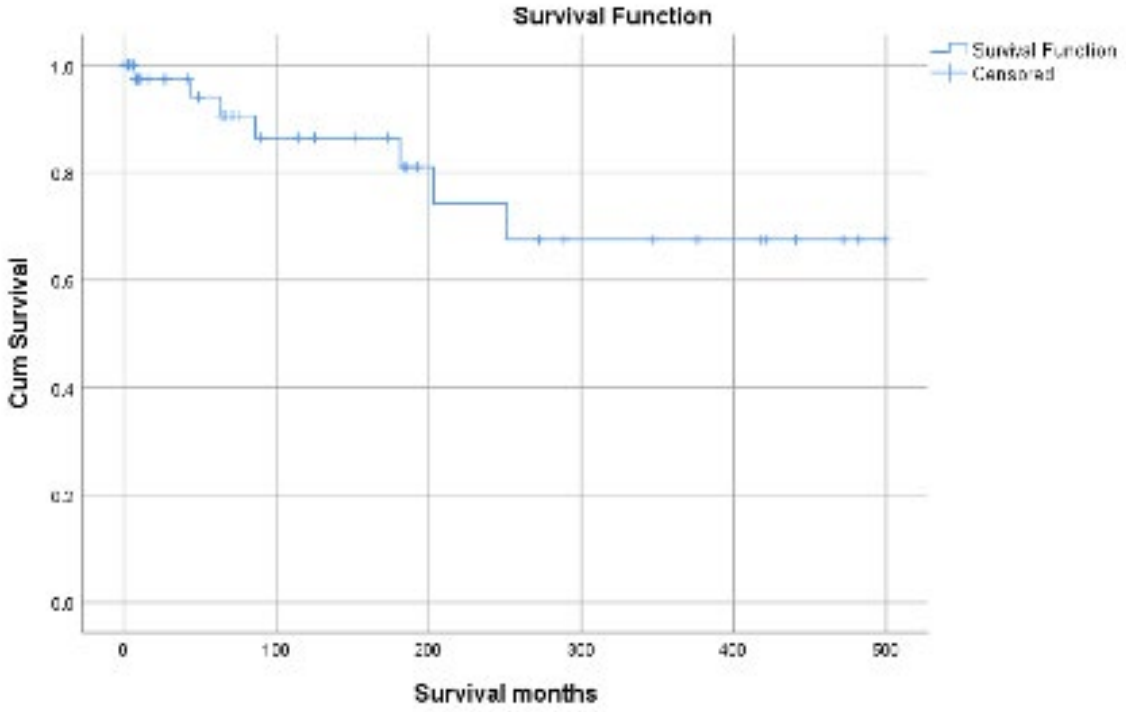


Figure 2. Overall survival estimates of patients with malignant hemangioendothelioma of bone remain relatively stable compared to disease-free survival until nearly 15 years, suggesting after this time patients this disease will more likely die from other causes than cancer.



Poster #278 3467407

RETREATMENT WITH FIRST LINE DRUGS IN MULTIPLY RELAPSED OSTEOSARCOMA

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Objective: Doxorubicin, Cis-platinum and Methotrexate [MAP] have been used since 1986 as the standard of care to treat osteosarcoma (OST). Relapsed OST have no standard 2nd or 3rd line therapies. In general practitioners try one of a handful of agents (interferon, ifosfamide, etoposide, or novel immunotherapies, bisphosphonates, or targeted agents) that have shown limited efficacy in OST and avoid repeating previous agents. However in a multiply relapsed patient retreatment with an agent know to have previously worked, when other options have been exhausted, may be reasonable. For example intra-arterial cis-platinum has been successful used as retreatment in several cases (Epelman S, Cancer, 1990;66(4):801-5) and a review by St. Jude found some patients responded to re-exposure to previous drugs in OST, usually doxorubicin. Retreatment with the same drugs is common in pediatric leukemia. However the convention, unproven, in treatment for sarcoma has been to never reuse the same drugs for fear of inducible resistance. We report 2 cases of multiply recurrent, progressive OST, retreated with first line drugs with a demonstrable clinical and palliative objective response.

To highlight successful treatment of relapsed OST with retreatment using first line drugs.

Methods: We reviewed PubMed and Google Scholar using keywords: "osteosarcoma," "retreatment," "methotrexate." The search was limited to the English language.

Results: We found no reported cases of response or non-response to re-exposure for relapsed OST in the selected databases, to MTX, Doxorubicin, or cis-platinum.

Case #1: At the time of diagnosis our patient was a 17-year-old female with metastatic osteosarcoma to the lungs and bone. At presentation she had pain at sites of metastasis and palpable tumors in her bones. The presenting alkaline phosphatase level was 1880 u/L. The patient was successfully treated with "MAPIE" (HDMTX, Adriamycin, cis-platinuum, ifosfamide, etoposide) and aggressive surgical resection of primary, bone and lung tumors and achieved radiological and clinical remission with an alkaline phosphatase level of 42 u/L. 12 months post-chemotherapy, the patient relapsed in the lungs. The patient was treated with denosumab for 6 cycles but progressed and also progressed on doxorubicin and nivolumab. At that point the alkaline phosphatase level rose to over 1200 and the patient requested to 're-try' MTX given the rapid elimination of pain she had had with MTX in the past. The patient experienced resolution of pain, dramatic decrease in size of the palpable bony vertebral mass, and decrease in alkaline phosphatase levels from 1248 to 889 with the 1st dose and from 889 to 571 after the 2nd dose. The patient tolerated therapy without any adverse effects [Figure 1]. Unfortunately no further doses of MTX were approved. The patient tried experimental therapy that did not work and died 3 months later.

Case #2: At time of diagnosis the patient was a 22 year old male with localized telangiectatic osteosarcoma of the right proximal fibula. Initial successful treatment consisted of resection and MAP. The patient had radiologic remission for 5 years until localized relapse of the right proximal tibia treated with surgery and zoledronic acid every 3 months. 15 months later a 2nd relapse of the right tonsil was treated with resection, proton radiation, and 6 cycles of ifosfamide and etoposide. 20 months later a 3rd relapse with lung progression treated with surgery, nivolumab, and targeted therapy failed. The patient started MAP, the exact therapy he had 10 years previous. At completion of 1st cycle, PET/CT showed significant necrosis of all metastatic lesions and 38% volume reduction of the left lung mass. The right apical lesion also had a 28% volume reduction. There was no evidence of new metastatic disease and patient reported alleviation of pain.

Conclusion: In a setting of limited or no options of treatment of relapsed osteosarcoma, retreatment of MAP and other first line drugs are worthy of consideration.

Figure 1

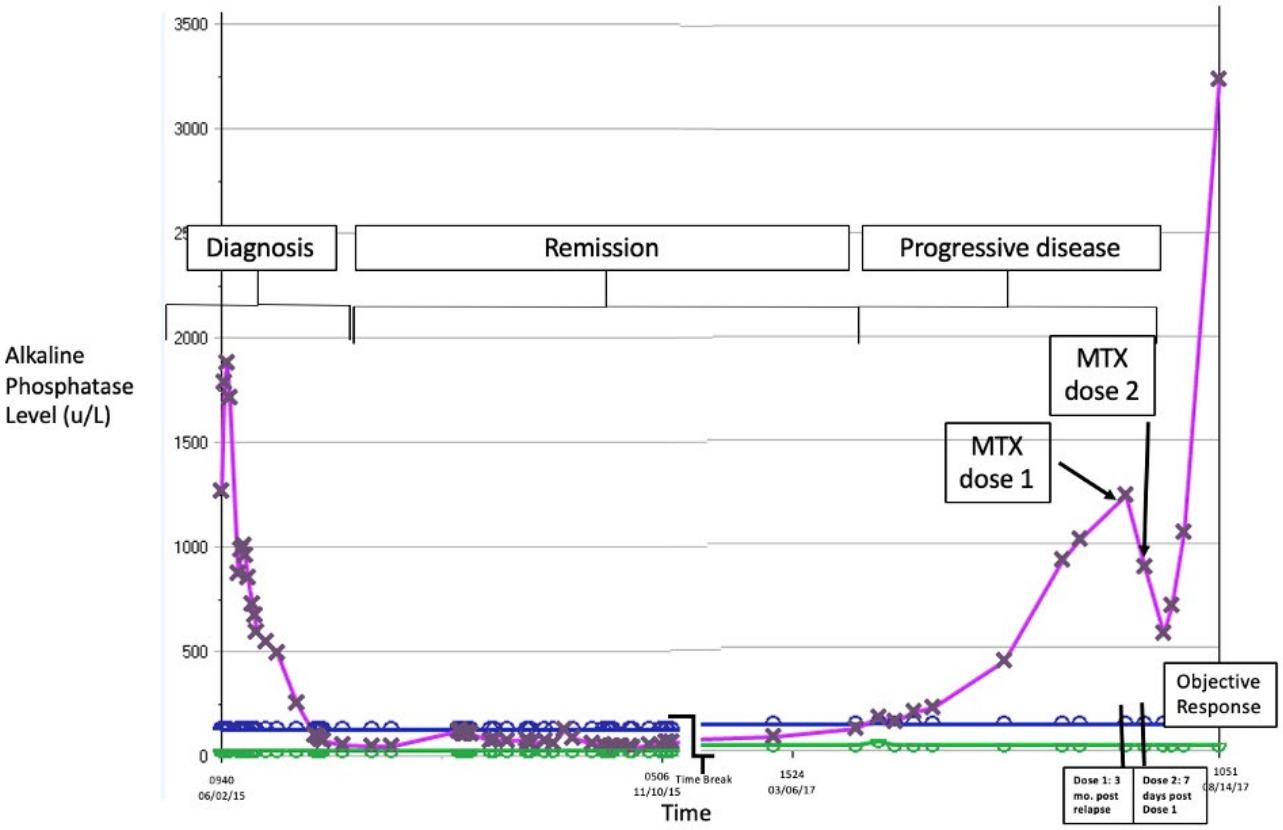
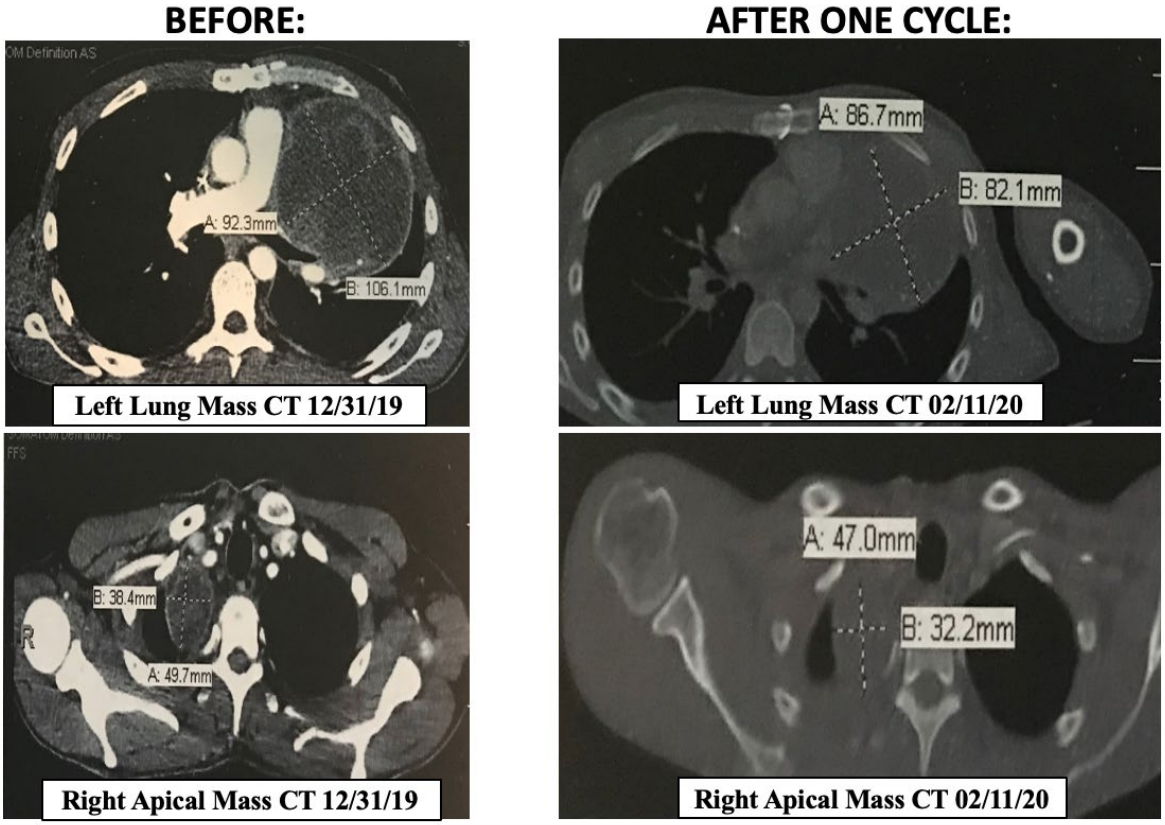


Figure 2



Poster #279 3467486

IS LOCAL RECURRENCE IN EXTREMITY SARCOMA JUST A LOCAL RECURRENCE, OR DOES IT IMPACT THE OVERALL SURVIVAL; NESTED CASE CONTROL STUDY FROM A SARCOMA REFERRAL CENTER.

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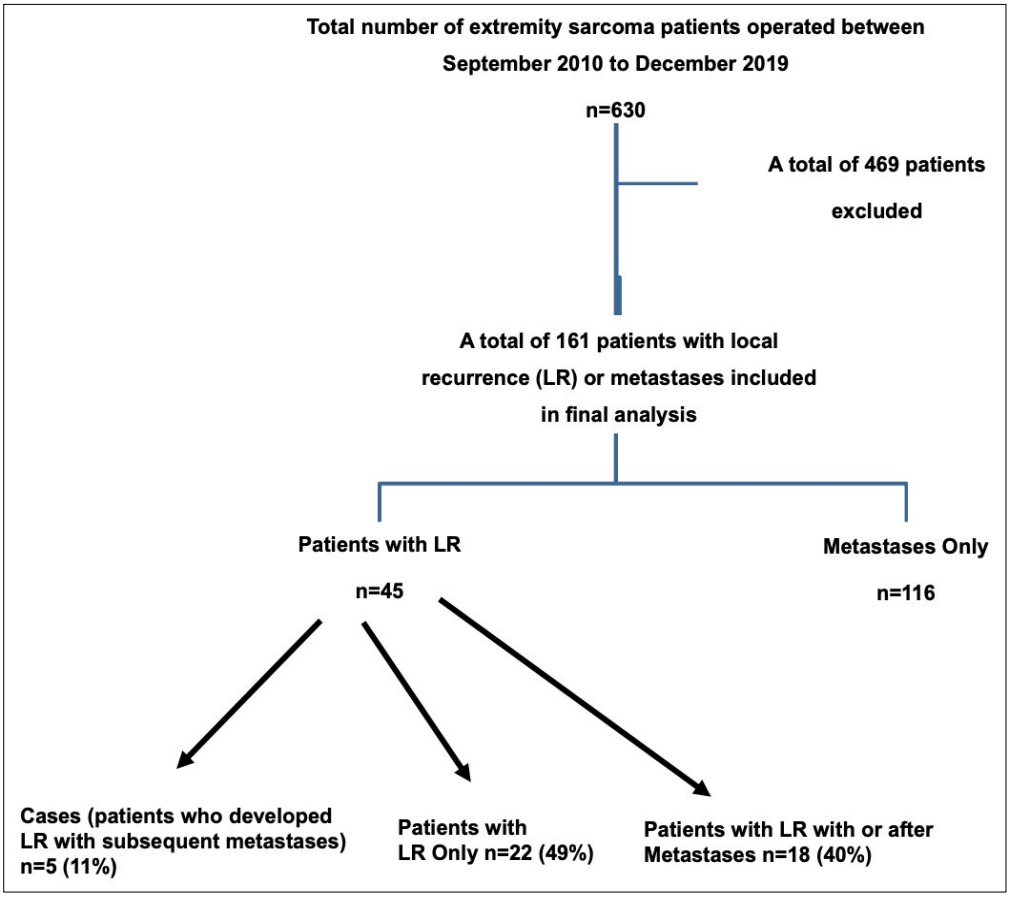
Objective: To determine the proportion of LR with subsequent metastasis (LRSM) in patients with bone and soft tissue sarcoma, whether the LR could have been the cause of the subsequent metastasis or was it just a LR which didn't affect overall survival.

Methods: Investigators identified patients who developed LR from an ongoing prospective cohort of bone and soft tissue sarcoma patients. Cases were patients who developed LRSM. We compared this group with 3 different groups; 1)LR in isolation, 2)LR with synchronous metastases, and 3)patients who developed metastases without LR. We excluded all patients who neither had LR nor metastases. Non-parametric analysis was used and results were reported in-line with the criteria of Strengthening The Reporting of Cohort Studies in Surgery (STROCSS).

Results: From the overall cohort of 630 bone and soft tissue sarcoma patients treated between September 2010 to December 2019, 161 patients met the inclusion criteria with overall incidence of LR in 45(7%) patients. Out of the 161 patients, 5 (3%) developed LRSM, 22 (14%) had LR in isolation, 18 (11%) had LR with prior or synchronous metastases while 116 (72%) patients developed metastases without LR. When comparing the cases (LRSM) to controls (LR in isolation), cases were younger 49±22 Vs 67±27years. Moreover, cases developed metastases after a median of 12.5(4-19) months. Bone sarcoma patients were 8.5 times likely to develop LRSM than soft tissue sarcoma OR;(95%CI)8.5(1.3-58.8). However, surgical margins, tumor grade and radiotherapy were not associated with the LRSM. Overall survival was highest for the LR in isolation group followed by the LRSM patients and worst for the patients who had LR with synchronous metastases at 2 and 5 years.



Conclusion: Developing LR with subsequent metastases is very rare, not related to the surgical margin but may be associated with worse survival as compared to LR in isolation. In 11% of cases, the LR preceded disseminated disease and raises the question of whether the LR could have been the cause of the subsequent metastasis. The answer to this question has implications regarding surgical margins, borderline limb salvageable presentations, functional preservation, and the use of radiation. We recommend further studies with a larger sample size to determine the factors associated with such an outcome.

Poster #280 3467593

NOVEL SCORING CRITERIA FOR PREOPERATIVE PREDICTION OF NEOADJUVANT CHEMOTHERAPY RESPONSE IN OSTEOSARCOMA: A RETROSPECTIVE COHORT STUDY FROM A SARCOMA CENTER

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Objective: While a better tumor response to chemotherapy can allow for a closer margin, function preservation, and a limb-sparing surgery in osteosarcoma, the response to chemotherapy is not known until after the surgery. The objective of the study was to identify clinical and radiographic factors following neoadjuvant chemotherapy, but prior to the tumor resection, that may aid in predicting a poor or favorable response to the treatment.

Methods: Investigators identified patients who had osteosarcoma from an ongoing cohort of extremity sarcoma patients. Our population on interest was patients who had osteosarcoma and managed with neoadjuvant chemotherapy between September 1, 2010, and February 1, 2020. We assessed post-chemotherapy tumor ossification on plain radiographs, tumor growth on sequential MRIs, and the presence of pain which was measured on the Visual Analog Scale. Our primary outcome was percent necrosis which categorized as a good response when necrosis is >90% and bad response when necrosis is <90% on the final histologic specimen. Non-parametric analysis was used and results were reported in-line with the criteria of Strengthening The Reporting of Cohort Studies in Surgery (STROCSS).

Results: From the overall cohort of 630 extremity sarcoma patients treated in the study period, 43 patients met the study criteria. A favorable response to treatment (>90% tumor necrosis) occurring in patients with a decrease in tumor size (change of 5mm), an increase, and no change in size were 9(69%), 1(9%), 4(21%), respectively with p value <0.01. Out of 25 patients with no pain and 18 with pain, 10(40%) and 4(22%), respectively, had a favorable response to treatment p value <0.01. Tumor ossification on plain radiographs was not associated with the outcome.

Conclusion: Among the predictive factors, only change in tumor size was significantly associated with a favorable response to neoadjuvant chemotherapy. Further investigation may determine whether pain or tumor ossification may aid in predicting neoadjuvant chemotherapy response rates in osteosarcoma. Such studies have implications regarding surgical margins, borderline limb salvageable presentations, and functional preservation. We recommend further studies with a larger sample size to determine the factors associated with such an outcome.

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