Molecular Therapy
Oncology
Meeting report

Progress in sarcomas: Highlights from the 2023 annual meetingof the Connective Tissue Oncology Society

Timothy P. Cripe,[1,2] Ryan D. Roberts,[1,2] Dawn S. Chandler,[1] Bhuvana A. Setty,[2] Sonja Chen,[3] Archana Shenoy,[3] Akila S. Venkataramany,[1,4,5,6] Emily M. Ringwalt,[1,7] Thomas Scharschmidt,[8] Thomas Utset-Ward,[8] David J. Konieczkowski,[9] Valerie P. Grignol,[10] Joel D. Beane,[10] Samantha M. Ruff,[10] and Raphael E. Pollock[10]

INTRODUCTION

Sarcomas comprise a wide range of diverse cancers of the bone and soft tissues, with ~100 different types as classified by the World Health Organization.[1,2] Sarcomas arise in any organ at any time, throughout the lifespan, and, depending on the specific type, can be treated with many known types of cancer therapies, including surgery, radiation, chemotherapy, targeted therapy, and immunotherapy. Care teams thus require multidisciplinary pediatric and adult expertise.

The Connective Tissue Oncology Society (CTOS), an international organization comprised of researchers, industry representatives, healthcare providers, and patient advocates focused on advancing care for sarcomas, held their 2023 annual meeting in Dublin, Ireland, November 1–4, 2023, providing a forum for the sharing of data, ranging from basic science to clinical outcomes across continents. The themes of the 2023 meeting included new understandings in biology and genomics, new diagnostics, advances in targeted therapies and immunotherapies, and surgical innovations. Although it is impossible to capture all of the issues presented at such a large, multidisciplinary conference, here, we summarize selected sessions, discussions, abstracts, and presentations to increase the reach of the latest knowledge and ongoing challenges with understanding biology and devising improved treatment for sarcomas.

Sarcoma of the year: Small, round blue cell tumor

The designated sarcoma of the year for the 2023 CTOS meeting was the small, round blue cell tumor (SRBCT). Thematically, as is true for sarcomas in general, SRBCT represents an array of different genetic subtypes, including Ewing sarcoma and others. The oral and poster presentations included a variety of round cell sarcomas, with a special focus on ultrarare round cell sarcomas that were previously grouped under undifferentiated round cell sarcomas (URCS) or Ewing-like sarcomas. The current understanding is that URCS comprises several tumor types diagnostically distinguishable by molecular testing. Emanuela Palmerini (Bologna, Italy) presented a retrospective analysis of 234 patients treated at 31 sarcoma centers worldwide from The Graceful Project, which highlighted that the vast majority of tumors can be reclassified as *CIC* rearranged sarcomas, followed by *BCOR* sarcomas and others within a small subset that remain unclassified. They also highlight the nonuniform treatment approaches to these tumors across institutions and the need for prospective multi-institutional studies in this realm. The key takeaway remains that URCS is a diagnosis that can be further refined with molecular testing, paving the way for standardized and/or targeted therapies to evolve.

Katherine Janeway (Boston, MA) delivered this year's Herman-Suit Lecture in recognition of her foundational contributions to understanding the genomic landscapes of pediatric sarcomas and using genomic characterization to guide therapy decisions. In her address, she summarized the findings of the PROFILE, iCAT, and Pediatric MATCH trials, which enrolled high proportions of sarcoma patients. These studies have established the utility of sequencing at diagnosis, showed how sequencing can complement other modalities to enhance the accuracy of diagnostic workups, identified an increasing number of fusion oncogene drivers in pediatric sarcomas, demonstrated a high prevalence of constitutional predisposition mutations in patients with sarcomas, and opened the door to defining biologically distinct subtypes of Ewing sarcoma and osteosarcoma. Her presentation emphasized the necessity of collaborative and multi-institutional initiatives to improve clinical implementation, data acquisition, and ongoing research as we seek to understand the implications of this work. She emphasized studies exploring direct patient engagement to enhance participation in these (and other) clinical trials.

The oral session also included studies on SRBCT characterization as well as clinical and preclinical therapeutic development.

[1]Center for Childhood Cancer Research, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH, USA; [2]Division of Pediatric Hematology/Oncology/BMT, Department of Pediatrics, The Ohio State University, Columbus, OH, USA; [3]Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus, OH, USA; [4]Biomedical Sciences Graduate Program, The Ohio State University, Columbus, OH, USA; [5]Medical Scientist Training Program, The Ohio State University, Columbus, OH, USA; [6]Center for RNA Biology, The Ohio State University, Columbus, OH, USA; [7]Molecular, Cellular, and Developmental Biology Graduate Program, The Ohio State University, Columbus, OH, USA; [8]Department of Orthopaedic Surgery, Nationwide Children's Hospital, Columbus, OH, USA; [9]Department of Radiation Oncology, The Ohio State University, Columbus, OH, USA; [10]Department of Surgical Oncology, The Ohio State University Wexner Medical Center, Columbus, OH, USA

Correspondence: Timothy Cripe, MD, PhD, Center for Childhood Cancer Research, Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH, USA.
E-mail: timothy.cripe@nationwidechildrens.org

Mehdi Breahmi (Lyon, France) discussed the clinical, biological, and molecular characterization of PATZ1-rearranged sarcomas. In their cohort of 16 patients, they used whole-exome RNA sequencing alongside clinical and pathology data to identify prognostic factors, including stage, Ki67 expression level, and RNA cell cycle (G2-M transition). The authors concluded that these are ultrarare tumors and are biologically different from Ewing sarcoma. Waisse Waissi (Lyon, France) presented preclinical data on exploiting replication stress as a novel therapeutic target in Capicua transcriptional repressor (CIC)-rearranged sarcomas. They found that targeting replication stress through ataxia telangiectasia and Rad3-related (ATR) inhibition decreases cell proliferation and tumor growth in CIC-DUX4 sarcomas. In addition, ATR inhibition radiosensitizes these tumors. Anthony Cillo (Pittsburgh, PA) presented data on pembrolizumab modulation of the Ewing tumor microenvironment. Although pembrolizumab therapy showed little clinical response, he and his colleagues used matched pre- and posttreatment samples to elucidate the protein expression patterns and "cellular neighborhoods" that contributed to treatment response and may indicate immunotherapeutic opportunities. Patrick Grohar (Philadelphia, PA) presented exciting preliminary results from the SARC037 clinical trial in which trabectedin administered as a 1-h infusion (as opposed to the traditional 24-h infusion) in combination with low-dose irinotecan showed antitumor activity and reversal of the EWS-FLI1 transcriptome in patients with Ewing sarcoma. In addition, circulating tumor DNA (ctDNA) trends were consistent with progression-free survival. Surinder Kumar (Miami, FL) demonstrated that sirtuin 5 regulates EWS-FLI1 and histone succinylation and may be a targetable therapeutic vulnerability. This session provided insight into the characterization of and potential therapeutics for several types of SRBCT.

Up for debate: Should care be limited only to high-volume centers and approved drugs?

The CTOS meeting is always lively when it comes to controversies in the field. Two organized debates at the 2023 meeting with audience voting featured spirited conversations about the effect of sarcoma centers and drugs with/without regulatory approval on sarcoma patient care. The first debate, headed by Sylvie Bonvalot (Paris, France) and Jeffrey Farma (Philadelphia, PA), raised the issue of whether complex sarcoma surgeries should be performed only in qualified centers with adequate sarcoma patient surgical volumes. Both speakers first acknowledged that the definition of a high-volume or low-volume center varies widely, so further clarity in guidelines may be required for global discussions on this topic. Bonvalot pointed out that high-volume centers have a wealth of expertise and knowledge resulting from exposure to more sarcoma cases, and this expertise results in better clinical outcomes for patients regardless of the cancer type, especially for primary tumors. Although mitigating factors such as environment (academic vs. community settings) and insurance must be considered in patients' care plans, high-volume centers have more highly trained multidisciplinary teams whose fellowship and experiences contribute significantly to surgery and treatment success. Farma countered that limiting sarcoma surgeries to high-volume centers is not possible or practical. Some published studies[3] have shown that although high- and low-volume centers have variations in care, patients exhibit no differences in tumor recurrence or survival. Importantly, since not all patients have financial or geographic access to high-volume centers, mandating centralization may lead to drastic inequalities in care and poorer outcomes. The debaters agreed that access to high-volume centers is unattainable for many and stressed the importance of improving education, sarcoma episodes of care, and pathway programs across all centers.

The second debate, led by Herbert H. Loong (Hong Kong, China) and Robin L. Jones (London, UK), posited that drugs without regulatory approval for sarcomas should not be used for treatment except in clinical trials. Loong emphasized that although clinical trials have improved the treatment of many cancer types, they remain flawed in terms of low patient enrollment and disparities in geographic distribution, among other issues. Furthermore, regulatory approval is notoriously slow and may not be congruent with available evidence-based knowledge for several years. By potentially limiting unapproved drugs to clinical trials, most patients would not have access to viable treatment options for their sarcomas. Therefore, the sarcoma providers' judgment should be at the forefront of patient care when unapproved or off-label drugs are included in the treatment regimen. This informed yet flexible decision making surrounding the application of these therapies will move the field forward. To rebut Loong's position, Jones highlighted that approval status for different drugs varies with geography, and providers may face challenges when trying to prescribe off-label medications in countries with stricter healthcare regulations. In addition, the lack of published research studies and safety data to support the use of unapproved drugs can raise the cost of healthcare and affect economic sustainability. Both speakers resolved that achieving a balance between real-world evidence and timely governmental approval is a problematic but lofty goal. Sarcoma specialists must communicate the successes and failures they observe in the clinic and collaborate to advance scientific understanding, clinical decision making, and governmental approvals.

Historical clinical trials

Data mining from historical trials can still be informative to modern clinical practice. Odion Binitie (Tampa, FL) presented results from the Children's Oncology Group report on INT-0133 and EURASMOS-1 data looking at early local progression (ELP) during the induction of chemotherapy in patients with localized nonmetastatic osteosarcoma. They found that these patients exhibited a 5-year postinduction survival close to 50%, which is worse than patients without ELP and even those with poor histologic response.

Dimosthenis Andreou (Graz, Austria) analyzed EURASMOS-1 data to evaluate the effect of treatment delays on the prognosis of high-grade osteosarcoma patients. This team observed that the induction of chemotherapy within 3 weeks of diagnostic

biopsy is sufficient to ensure the best outcomes, but delays during induction chemotherapy and a delayed start of consolidation chemotherapy after surgery are independently associated with poorer patient survival.

Targeted therapy clinical trials

The Medical and Pediatric Oncology Trials session highlighted numerous innovative and exciting ongoing clinic trials. Mark Agulnik (Duarte, CA) presented a phase 2 study of cabozantinib and temozolomide in patients with unresectable or metastatic leiomyosarcoma (LMS) and other soft tissue sarcomas (STSs). The group hypothesizes that dual targeting of vascular endothelial growth factor and c-MET pathways will result in clinical benefit when combined with an alkylating agent. The goal of the study is to determine 12-week progression-free survival for patients treated with combination therapy, which was reported at 74% for undifferentiated (u)LMS and LMS, with the majority treated thus far experiencing grade 3 and 4 hematologic toxicities and grade 3 hypertension, and diarrhea. Andy Livingston (Houston, TX) shared preliminary results from a phase 1 study of FHD-609, a bromodomain-containing protein 9 degrader, in patients with advanced synovial sarcoma or SMARCB1-loss tumors. They identified the maximal tolerated dose and observed preliminary evidence of clinical activity. Careful cardiac monitoring was warranted during this treatment due to notable cardiac adverse effects of abnormal electrocardiogram T waves and QT prolongation. Brian Van Tine (St. Louis, MO) presented data from a first-in-human study of KB-0742, an orally bioavailable inhibitor of CDK9, which drives oncogene transcription elongation. The therapy was deemed safe and feasible, with the most common adverse effect reported as nausea and vomiting in >10% of patients. With nearly half of patients experiencing stable disease, the authors concluded that this treatment demonstrates preliminary evidence of clinical activity in transcriptionally addicted sarcomas. Bernadette Brennan (Manchester, UK) presented data from an international randomized trial of the addition of zoledronic acid to consolidation chemotherapy in newly diagnosed Ewing sarcoma patients (EE2012 trial). This study included all of the patients from the Ewing sarcoma family of tumors with localized disease, pleuro-pulmonary metastasis, and/or other metastatic sites. The primary goal of the study was a frequentist superiority design including 400 patients to show a 10% improvement with the addition of zoledronic acid, with plans to combine data from the prior Ewing sarcoma 2008 trial. The authors reported that a combination of zoledronic acid failed to improve event-free or overall survival in Ewing sarcoma.

Immunotherapy clinical trials

The Immunology and Immunotherapy session focused on clinical trials for immunotherapies against various sarcomas. John Mullinax (Tampa, FL) reported his team's results from a phase 1 trial of lymphodepletion with tumor-infiltrating lymphocyte adoptive cell therapy followed by high-dose interleukin-2 in adolescent/young adult sarcoma patients. Most of the patients tolerated the therapy well; however, T cell clone contraction and high disease burden limited the objective responses. Brian Van Tine (St. Louis, MO) used afamitresgene autoleucel (afami-cel), an autologous T cell receptor T cell therapy targeting MAGEA4 in HLA-A*02 patients with advanced synovial sarcoma in the phase 2 SPEARHEAD-1 trial. The 39% of patients with a RECIST-determined response and those with higher afami-cel cellular persistence exhibited improved overall survival. Breelyn Wilky (Denver, CO) reported on the first-in-human combination of botensilimab (anti-programmed cell death protein 1 [PD-1] antibody) and balstilimab (anti-cytotoxic T lymphocyte-associated protein 4 [CTLA4] antibody) in patients with metastatic sarcoma, which showed promising disease stabilization and responses with manageable adverse effects. In another combinatorial trial, Nadia Hindi (Madrid, Spain) presented the results from expanding the vascular sarcoma cohort for the phase 2 trial of sunitinib and nivolumab and compared the outcomes to other immunotherapy combinations and systemic therapies. Although the majority of patients did not achieve a 6-month progression-free survival rate, the combination was comparable to previous tyrosine kinase inhibitor monotherapy. To end the session, Shantanu Banerji (Winnipeg, Canada) showed that the phase 2 trial of durvalumab (anti-PD-ligand 1 antibody) combined with tremelimumab (anti-CTLA4 antibody) in patients with osteosarcoma and undifferentiated pleomorphic sarcoma failed to meet its primary endpoints, but indicated future exploration of the biomarkers in responding tumors. Ultimately, this section updated the field on combinatorial immunotherapy trials in sarcoma and highlighted the work remaining ahead.

Preclinical studies to inform future clinical trials

The Preclinical Models and Translational Research session of the 2023 CTOS meeting undertook a wide array of preclinical advances, including mouse models, test therapeutics, genomic analysis of treated tumors, and engineering advances with surgical tools to predict better margins during tumor resection. Poul Sorensen (Vancouver, Canada) showed that osteosarcoma cells become reliant on increased levels of nuclear factor erythroid 2-related factor 2 (NRF2) to deal with the oxidative stress that is part of the metastatic cascade. Hence, treating osteosarcoma cells by targeting mRNA translation with the CR-1-31B inhibitor of EIF4A1/2 blocked the antioxidative response in metastatic cells, decreased NRF2 levels, and inhibited lung metastasis in mice. These findings have spurred the testing of clinical-grade inhibitors of EIF4A1/2. Amit Sabnis (San Francisco, CA) identified the ubiquitin hydroxylase UCHL5 as a selective dependency in fusion-positive rhabdomyosarcoma due to its induction by the fusion protein of replicative stress, and loss of UCHL5 increases the efficacy of drugs that induce replicative stress. Nathan El-Ghazzi (Bordeaux, France) discussed the cytotoxicity of the antibody/drug conjugate ADCT-601 against the AXL tyrosine kinase receptor in 11 STS cell lines but not 13 epithelial cell lines. The drug caused double-stranded breaks in DNA and synergized with ataxia telangiectasia mutated and ATR inhibitors. The combination also showed antitumor efficacy in a mouse model, further suggesting additional preclinical testing of this combination. Filemon Dela Cruz (New

York, NY) sequenced the transcriptome from 112 pediatric sarcoma samples and 67 patient-derived xenografts to generate a gene regulatory network and identify potential therapeutic targets. An array of predicted drugs was tested and shown to slow tumor growth of specific sarcomas in early *in vitro* studies. Overall, the molecular, genetic, and engineering approaches described all of the model systems and tools that have been used to move the field closer to better therapies for improved outcomes in sarcoma patients.

The challenge of tumor heterogeneity in gastrointestinal stromal tumors (GISTs)

The GIST session focused primarily on identifying and/or treating subsets of patients based on tumor heterogeneity. Adam Burgoyne (La Jolla, CA) began the session by presenting an update to the current phase 2 clinical trial of temozolomide for the treatment of patients with advanced succinate dehydrogenase (SDH)-deficient GIST, a rare subtype of this disease. Although this multicenter study did not meet its primary endpoint (overall response rate), it did demonstrate that temozolomide had an acceptable safety profile and showed a higher efficacy signal than in previous studies with tyrosine kinase inhibitors or demethylating agents in the SDH-deficient GIST population. Priscilla Merriam (Boston, MA) also presented preliminary data from a phase 2 clinical trial studying rogaratinib (fibroblast growth factor receptor inhibitor) in patients with SDH-deficient GIST. They found that rogaratinib had an acceptable safety profile and demonstrated promising activity in this patient cohort. In the future, correlative studies from these clinical trials evaluating the genomic landscape of tumor biopsies will help to efficiently accrue patients in multicenter trials. In line with that, Ashwyn Sharma (San Diego, CA) presented his and colleagues' findings that investigated the intra- and intertumor cell heterogeneity of GIST to determine whether all GIST truly arise from the interstitial cells of Cajal, given the genomic diversity of these tumors. Based on these findings, they propose that other cell types may give rise to GIST based on location within the digestive tract and varying mutations. Since many sarcomas have been reclassified over time by using genomic profiling and histology, these studies will increase our understanding of the disease and help us choose the correct targeted therapies for a given patient. Resistance to targeted therapies remains an issue, and Sebastian Bauer (Essen, Germany) presented a genomic analysis of 25 samples from patients exhibiting resistance to fourth-line treatment of GIST with ripretinib (a KIT kinase inhibitor). He found, in some cases, dual mutations in the KIT binding pocket and activating loop. Thus, he suggested that combination therapy with ripretinib and sunitinib (multitargeted receptor tyrosine kinase inhibitor) would synergize against the resultant clones possessing the mixed mutations.

Retroperitoneal and abdominal sarcomas

The Retroperitoneal Sarcoma (RPS) session this year included a number of exciting presentations that focused on both clinical and translational research, with the common goal of improving our ability to predict prognosis. Highlights from this session included Mark Fairweather (Boston, MA), who presented the first study from the Transatlantic Australasian Retroperitoneal Sarcoma Working Group prospective sarcoma registry that created an RPS surgical complexity score to predict postoperative morbidity in patients undergoing primary RPS. With a database of 1,207 patients, they created a scoring system incorporating both patient (e.g., comorbidities, age, neoadjuvant therapy) and operative factors (points awarded based on organ resection and reconstruction). Future studies will include external validation of the scoring system. Dario Callegaro (Milan, Italy) presented an update of the Sarculator nomogram that now incorporates the effect of a low- vs. high-volume center on overall and disease-free survival. They suggested the differences may be an impetus to refer patients with RPS preferentially to high-volume centers. Finally, George Li (New York, NY) used clinicopathologic factors and genomic analyses with a targeted sequencing panel to identify histologic subtypes of well-differentiated liposarcoma that had prognostic implications. Continued coordination between large centers to build databases of clinicopathologic factors and tissue for analysis is necessary to improve patient selection for surgery, radiation, and chemotherapy treatments, as well as long-term outcomes for these patients. Creating a multicenter repository of already-sequenced tissue may help further exploratory studies for this rare tumor type.

Genomics and biomarkers

With the conclusion of Children's Oncology Group Trial ARST1431 for patients with intermediate-risk rhabdomyosarcoma (RMS), multiple authors presented data from a central pathology review. Archana Shenoy (Columbus, OH) provided an analysis of RMS with PAX7 fusion and distinct morphologic association with mixed embryonal and alveolar RMS. Sonja Chen (Columbus, OH) described an immunohistochemical panel to predict FOXO1 fusion RMS in resource-limited settings or small biopsy samples. Finally, Michael Arnold (Denver, CO) described rare cases of RMS with Burkitt-like morphology associated with high amplification of MYCL.

Genomic studies were also front and center in osteosarcoma. Jose Espejo Valle-Inclan (London, UK) showed data suggesting that whole-genome doubling and complex genome rearrangements were frequent oncogenic events that can evolve as osteosarcoma lesions develop. Interestingly, their analysis suggests that many of the complex rearrangements in osteosarcoma have structural patterns that cannot be explained by any known mechanisms. Roelof van Ewijk (Utrecht, the Netherlands) presented data validating an RNA-based osteosarcoma risk signature initially defined by the Gaspar group. Although their data supported the risk-stratifying value of the signature, they also found that the expression of these signature-driving genes can change in response to therapy—a finding of uncertain significance at this time. Hannah Bender (Boston, MA) described age-related differences in gene expression with more frequent alterations in DNA repair in children and adolescents, whereas young adults more often showed mutations related to cell-cycle genes, suggesting that different subtypes exist across the age spectrum. Wajih Jawher (Montreal, Canada) identified *EZHIP*

overexpression in aggressive osteosarcoma, and Natacha Entz-Werle (Strasbourg, France) reported improved survival in patients with an osteoblastic-gene signature. Ryan Roberts (Columbus, OH) presented data identifying interactions between epithelial cells and disseminated tumor cells in the lung that can induce a chronic wound reaction, driving the deposition of a fibronectin-rich, scar-like matrix essential for the formation of a metastatic niche. Interruption of this fibrogenic signaling reduced metastases, a strategy that could be translated to human clinical trials.

In other STSs, biomarker identification was a highlight of various studies. Yuen Bun Tam (London, UK) used proteomics to identify characteristic protein signatures in adolescent and young adult patients. Yongsung Kim (Seoul, Korea) identified *ARHGEF4* overexpression as a possible biomarker correlated with infiltrative and expanding histologic growth patterns in undifferentiated pleomorphic sarcoma and myxofibrosarcoma. Yeh Chen Lee (Randwick, Australia) reported actionable fusions in a subset of gynecologic sarcomas. Naoya Nakahashi (Sapporo, Japan) found that increased expression of the poliovirus receptor (CD155) in malignant peripheral nerve sheath tumor was highly correlated with proliferation, colony formation, migration, and invasiveness in cell lines.

Overall, the utility of genomics, methylation profiling, and epigenetics cannot be overstated in determining the underpinnings of integral biological drivers in many bone and STSs. Although, at this time, only a subset can be targeted, it is clear that therapeutics will be modeled after the unique biology of these rare tumors.

Surgical innovations

This year, CTOS introduced a new operative and procedural video session geared toward the exchange of surgical innovations and techniques with the aid of video. Complex surgical techniques included periacetabular fixation, rotationplasty, and isolated limb perfusion. Joel Werier (Ottawa, Canada) and Shintaro Iwata (Tokyo, Japan) shared techniques for using three-dimensional technology, such as virtual reality, virtual surgical planning, and mixed-reality aids in sarcoma surgery. Chandrajit Raut (Boston, MA) presented the results of a survey distributed to surgeons in the Trans-Atlantic Retroperitoneal Sarcoma Working Group and CTOS aimed at defining the profile and minimum requirements of a "sarcoma surgeon." There were three times as many surgical oncologist as orthopedic oncologist respondents. Among the surgical oncologists, expertise in colorectal, hepatico-pancreatico-biliary, and vascular surgery was considered an important part of a sarcoma surgeon's training. Most respondents indicated that sarcoma surgeons should perform at least 30 sarcoma resections per year.

Multiple presentations and posters centered around surgical innovations for detecting tumor residuals and margins intraoperatively. Kurt Weiss (Pittsburgh, PA) presented the use of indocyanine green (ICG) fluorescence imaging administered intravenously 1 h before surgery and found a stain rate of 94% in bone and soft tissue malignancies and an accuracy of 49% for predicting tumor residuals using intraoperative fluorescence imaging. This complemented the poster by Sallu Dawo (Newcastle, UK) applying the ICG technology to bone and soft tissue metastases where all tumors were found to fluoresce, and the surgeons found fluorescent intraoperative guidance helpful 70% of the time. Maximillian Kerkhoff (Essen, Germany) presented chorio-allantoic membrane model results for a photodynamic diagnostic and therapeutic technology that showed promise in defining tumor margins through fluorescence from protoporphyrin IX and adjuvant treatment of the tumor bed through the photodynamic production of reactive oxygen species that fragmented tumor blood vessels and led to cell death. Finally, Keila Torres (Houston, TX) described the MasSpec Pen, which samples tissues and analyzes them in real time in the operating room with a mass spectrometer. The nondestructive tool that gives near-real-time mass spectrometry signatures will be tested in the operating room in an attempt to confirm clean tumor resections during the primary surgery to decrease tumor recurrence.

Radiotherapy (RT)

Rick Haas (Amsterdam, the Netherlands) delivered the annual Nina Axelrad Lecture on the historical origins and modern applications of fractionation in RT. In its infancy, radiation therapy was given in multiple fractions rather than all at once, not for biological or clinical reasons, but to let the cathode ray tubes cool down between treatments. Subsequently, the biological basis for fractionation—allowing repair of nearby normal tissues between fractions, thereby decreasing overall treatment toxicity—came to be appreciated as a central tenet of radiobiology. In the modern era, technological improvements have reduced the normal tissue irradiated during each treatment, thus permitting higher doses per fraction and treatments to be completed in fewer total fractions (hypofractionation). Fractionation and its application continue to be a central consideration in modern RT. For example, Dr. Haas' recent DOREMY study[4] demonstrated favorable results with deescalating preoperative RT dose for myxoid liposarcoma, exemplifying his dictum of "less when possible, more when needed." The importance of fractionation was highlighted by a number of other studies, including Andrew Bishop's (Houston, TX) presentation of favorable long-term toxicity results of the prospective HYPORT study of moderately hypofractionated (15 fractions) preoperative RT for STSs. Other presenters included Brian O'Sullivan (Toronto, Canada), detailing promising results of preoperative RT for head and neck STSs; Danny Indelicato (Gainesville, FL), with favorable results of preoperative RT in patients with localized Ewing sarcoma treated on AEWS1031, and Ahsan Farooqi (Houston, TX), describing institutional outcomes with preoperative RT and surgical reresection following unplanned excision of STS. Highlighting the need to explore further biological correlates of fractionation, Meena Bedi (Milwaukee, WI) reported a potential increase in tumor-infiltrating lymphocytes during ultrahypofractionated (5 fractions) as opposed to conventionally fractionated (25 fractions) preoperative RT. Finally, Everett Moding's group (Palo Alto, CA) presented impressive work using multiregion spatial genomic profiling to reveal both an increase in

intratumoral heterogeneity during preoperative RT and the ability to monitor the evolution of these subclones via ctDNA.

Summary and conclusions

Sarcomas remain a challenge in part because there seems to be an ever-growing number of different types and variations. Nevertheless, we are gaining an increasing knowledge of genomic underpinnings, diagnostic refinements, and prognostic and predictive biomarkers. We continue to innovate by using conventional, targeted, immunologic, and radiologic therapies and inventing improved surgical techniques to positively affect patients and their quality of life. All of these was never more evident in one place and time than at the 2023 CTOS meeting.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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