11500 Oral Abstract Session

Pimicotinib in tenosynovial giant cell tumor (TGCT): Efficacy, safety and patient-reported outcomes of phase 3 MANEUVER study.

Xiaohui Niu, Vinod Ravi, Javier Martin Broto, Yong Zhou, Albiruni Ryan Abdul Razak, Ramy Saleh, Jingnan Shen, Tang Liu, Silvia Stacchiotti, Kamalesh K. Sankhala, César Serrano, Jing Wang, Yingqi Hua, Piotr Rutkowski, Xiaojing Zhang, Yi Feng, Tao Li, Giacomo Giulio Baldi, Hairong Xu, Hans Gelderblom; Department of Orthopedic Oncology Surgery, Beijing Ji Shui Tan Hospital, Beijing, China; The University of Texas MD Anderson Cancer Center, Houston, TX; Fundación Jimenez Diaz University Hospital, Madrid, Spain; Department of Orthopedics, West China Hospital, Sichuan University, Chengdu, China; Princess Margaret Cancer Center, Toronto, ON, Canada; Cedars Cancer Center, McGill University Health Center, Montreal, QC, Canada; Department of Musculoskeletal Oncology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; The Second Xiangya Hospital of Central South University, Changsha, China; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Precision NextGen Oncology and Research Center, Los Angeles, CA; Hospital Universitario Vall d'Hebron, Vall d'Hebron Institute of Oncology, Barcelona, Spain; Hunan Provincial People's Hospital, Changsha, China; Shanghai General Hospital, Shanghai, China; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Liaoning Cancer Hospital & Institute, Shenyang, China; The Second Hospital of Shanxi Medical University, Taiyuan, China; Zhejiang Cancer Hospital, Hangzhou, China; Department of Oncology, Hospital of Prato, Azienda USL Toscana Centro, Prato, Italy; Department of Orthopaedic Oncology Surgery, Beijing Ji Shui Tan Hospital, Peking University, Beijing, China; Leiden University Medical Center, Leiden, Netherlands

Background: TGCT is a rare, locally aggressive mesenchymal neoplasm, driven by the overproduction of colony-stimulating factor 1 (CSF-1), and is often associated with joint pain, swelling, stiffness and functional impairment. The high rate of recurrence and the significant tumor burden, particularly in the diffuse variant, highlight the necessity for an effective systemic treatment. Pimicotinib (pimi) is an oral, highly selective and potent small-molecule inhibitor of CSF-1 receptor (CSF-1R). We report the results from the double-blind Part 1 of MANEUVER, the first global Phase 3 trial to recruit TGCT patients (pts) from Asia, EU and North America (NA) who were candidates for systemic therapy. **Methods:** MANEUVER (NCT05804045) is a Phase 3, randomized, double-blind, placebo (pbo)-controlled trial evaluating efficacy and safety of pimi in pts with TGCT. In Part 1, pts received pimi 50 mg QD or pbo (2:1) for 24 weeks. Primary endpoint was objective response rate (ORR) by blinded independent review committee (BIRC) per RECIST v1.1 at Week 25. Key secondary endpoints included ORR by tumor volume score (TVS) and clinical outcome assessments (COAs) at Week 25: mean change from baseline in range of motion (ROM), worst stiffness, Brief Pain Inventory (BPI) worst pain and PROMIS physical function. Safety was also evaluated. **Results:** At the data cutoff of Sep 23, 2024, all of the planned 94 pts were enrolled (China = 45; EU = 28; NA = 21), with 63 randomized to pimi and 31 to pbo.Median age was 40.0 years (range: 18-69); 68.1% were female; disease location mainly in knee (50.0%), ankle (14.9%) or hip (13.8%). ORR by BIRC per RECIST v1.1 and TVS at Week 25 was significantly higher for pimi vs pbo (54% vs 3.2% and 63.5% vs 3.2%, respectively; both $p < 0.0001$). Statistically significant and clinically meaningful improvements were observed with pimi vs pbo for all COAs: active ROM (15.64 vs -0.07; $p = 0.0003$), worst stiffness (-3.00 vs −0.57; $p < 0.0001$), BPI worst pain (-2.32 vs −0.23; $p < 0.0001$) and PROMIS physical function (5.63 vs 2.23; $p = 0.0074$). Significantly more pain responders (BPI-30) were observed with pimi vs pbo (63.5% vs 16.1%; $p < 0.0001$). Treatment efficacy was consistent across pts from different regions and ethnicities. Most TEAEs were low grade, consistent with the known mechanism of action of CSF-1R inhibitors and led to a low rate of dose reduction (7.9%, 5/63 pts) and treatment discontinuation (1.6%, 1/63 pt). There was no evidence of cholestatic hepatotoxicity or drug-induced liver injury. **Conclusions:** MANEUVER is the first randomized pivotal study in TGCT to demonstrate > 50% ORR by RECIST v1.1 at Week 25 in a diverse, global patient population. Pimi produced statistically significant and clinically meaningful improvements in physical function and symptoms, representing an effective, well-tolerated and convenient daily treatment for patients with TGCT and addressing a critical unmet need. Clinical trial information: NCT05804045. Research Sponsor: Abbisko Therapeutics Co., Ltd.

11501 Oral Abstract Session

Anlotinib in combination with epirubicin followed by maintenance anlotinib versus placebo plus epirubicin as first-line treatment for advanced soft tissue sarcoma (STS): A randomized, double-blind, parallel-controlled, phase III study.

Yuhong Zhou, Xiaohui Niu, Yu Jiang, Bin LI, Wei Luo, Jilong Yang Sr., Xiaowei Zhang, Xianan Li, Zhengfu Fan, Yongchun Song, Renbing Jiang, Rutian Li, Meiyu Fang, Guofan Qu, Dongyuan Zhu, Di Wu, Wei Li, Zhen Huang, Jiating Hu, Xiaojing Wan; Zhongshan Hospital, Fudan University, Shanghai, China; Beijing Jishuitan Hospital, Beijing, China; Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; Xiangya Hospital of Central South University, Changsha, China; Department of Bone and Soft Tissue Tumor, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Hunan Cancer Hospital, Changsha, China; Beijing Cancer Hospital, Beijing, China; The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Affiliated Tumor Hospital of Xinjiang Medical University, Urumchi, China; The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China; Department of Rare Cancer & Head and Neck Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China; The Affiliated Tumor Hospital of Harbin Medical University, Harbin, China; Cancer Hospital of Shandong First Medical University, Jinan, China; The First Hospital of Jilin University, Changchun, China; Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; Beijing Jishuitan Hospital, Capital Medical University, Beijing, China; Chia Tai Tianqing Pharmaceutical Group Co., Ltd., Nanjing, China

Background: Anthracycline-based chemotherapy has been the standard first-line treatment for advanced STS for decades. The phase 3 ANNOUNCE trial failed to demonstrate an overall survival (OS) benefit with olaratumab plus doxorubicin compared to doxorubicin. Since 2020, fewer novel regimens emerged to challenge the first-line treatment. Anlotinib (ALTN), an anti-angiogenic oral multi-target tyrosine kinase inhibitor, first showed promising results in a phase II single-arm trial, the addition of ALTN to epirubicin (EH) followed by maintenance ALTN improved progression-free survival (PFS) in the first-line setting for STS patients (pts). Consequently, we conducted a nationalwide, randomized, double-blind, parallel-controlled, phase 3 trial comparing ALTN plus EH followed by ALTN maintenance versus EH combined with placebo (PBO) as first-line treatment for advanced STS pts in China. **Methods:** Eligible pts had previously untreated, pathologically confirmed, unresectable locally advanced or metastatic STS. Pts were randomized in a 1:1 ratio to receive either ALTN (12mg) orally once daily (2-week on/1-week off) plus EH (90 mg/m^2) intravenously once every 3 weeks up to 6 cycles, followed by maintenance ALTN (12mg) orally once daily (2-week on/1-week off) or PBO (0mg) orally once daily (2-week on/1-week off) plus EH(90 mg/m^2) intravenously once every 3 weeks up to 6 cycles, followed by maintenance PBO (0mg) orally once daily (2-week on/1-week off). The primary endpoint was PFS assessed by the blinded independent review committee according to RECIST 1.1. Secondary endpoint included OS, Objective Response Rate (ORR), Disease control rate (DCR) and safety. **Results:** A total of 272 pts were randomized: 135 to ALTN + EH arm, 137 to PBO + EH arm. As of February 15, 2024, after a median follow-up of 7.16 mo, ALTN + EH arm significantly improved PFS (HR 0.30 [95% CI 0.21-0.44]; $P < 0.001$; median 8.57 vs 3.02 mo), and ORR (17.8% vs 2.90%; $P < 0.001$) , DCR (79.3% vs 54.7%; $P < 0.001$) versus PBO + EH arm. The median OS was not reached in either arm (HR = 0.78 [95% CI: 0.49-1.25]). The benefit of ALTN + EH arm was observed across most subgroups tested, including leiomyosarcoma, synovial sarcoma and other pathological types. The incidence of Grade $\geq$3 adverse events (AEs) (69.6% vs 59.1%), AEs leading to discontinuation of treatment (3.7% vs 4.4%), fatal AEs (3.7% vs 3.6%) were similar between two arms. **Conclusions:** Anlotinib in combination with epirubicin followed by maintenance ALTN demonstrated a statistically significant and clinically meaningful PFS benefit compared to epirubicin alone in pts with previously untreated advanced STS, which could serve as a potential new first-line treatment for locally advanced or metastatic STS. The final OS outcomes are currently under ongoing follow-up. Clinical trial information: NCT05121350. Research Sponsor: None.

11502 Oral Abstract Session

Eribulin plus anlotinib in advanced soft tissue sarcoma (ERAS): Updates on efficacy and biomarkers.

Jie Liu, Yang Fu, Bin Wang, Zhike Li, Ying Wang, Jie Zhang, Tingwu Yi, Yaotiao Deng, Yu Jiang; Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; Department of Oncology, The First Affiliated Hospital of North Sichuan Medical College, Nanchong, China; Department of Oncology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China; Department of Oncology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; Department of Oncology, The People's Hospital of Leshan, Leshan, China

Background: This study provides an updated evaluation of the efficacy and biomarker analysis of combination therapy using eribulin, a microtubule dynamics inhibitor, and anlotinib, a multi-targeted tyrosine kinase inhibitor, in patients with advanced soft tissue sarcoma. **Methods:** In this multi-center phase II study (ERAS), patients received eribulin (1.1 mg/m^2 intravenously on days 1 and 8) and anlotinib (12 mg orally once daily on days 1-14) in 21-day cycles for 6-8 cycles, followed by maintenance therapy with anlotinib. Pre-treatment paraffin-embedded tumor samples were subjected to transcriptome sequencing analysis. The efficacy of the combination therapy in the ERAS study was compared to that of patients previously treated with anlotinib monotherapy. **Results:** As of the cut-off date of December 15, 2024, the median follow-up time was 17.8 months for 30 patients receiving combination therapy with eribulin and anlotinib (9 with leiomyosarcoma, 6 with dedifferentiated liposarcoma, and 15 with other types of sarcomas). In contrast, 87 patients received anlotinib monotherapy, with a median follow-up time of 43.3 months. This cohort comprised 28 patients with leiomyosarcoma, 8 with liposarcoma, and 51 with other types of sarcomas. After 1:2 propensity score matching analysis, compared to anlotinib monotherapy, the combination therapy of eribulin plus anlotinib resulted in a higher progression-free survival rate at 24 weeks (70.0% vs. 31.7%, P = 0.001), significantly improved median progression-free survival (8.5 vs. 4.0 months, P = 0.004), and extended overall survival (not reached vs. 18.4 months, P = 0.035) in patients with advanced soft tissue sarcoma. Transcriptomic data from patients treated with eribulin and anlotinib revealed that tumors with partial response or stable disease exhibited significantly higher levels of lipid metabolism compared to those with progressive disease. **Conclusions:** The combination therapy of eribulin plus anlotinib demonstrated superior efficacy compared to historical data from anlotinib monotherapy in patients with advanced soft tissue sarcoma. The lipid metabolism level in sarcomas could serve as a biomarker for the efficacy of this treatment regimen, potentially providing new insights into L-type sarcomas. Clinical trial information: ChiCTR2300067650. Research Sponsor: 1·3·5 project for disciplines of excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University.

Results of a 1:2 propensity score matching analysis.

Characteristic	Anlotinib monotherapy (*n* = 60)	Eribulin plus Anlotinib (*n* = 30)	*P* value
Age			0.549
≥65 years	9	6	
<65 years	51	24	
Gender			0.648
Woman	37	17	
Man	23	13	
Pathological subtype			0.654
Leiomyosarcoma/liposarcoma	33	15	
Other sarcomas	27	15	
Pathological grade			-
G1/Gx	0	0	
G2/G3	60	30	
Stage			0.096*
Locally advanced	5	7	
Metastatic	55	23	
Surgery history			-
No	0	0	
Yes	60	30	
Radiotherapy history			0.226
No	38	15	
Yes	22	15	
Chemotherapy history			>0.999*
No	6	3	
Yes	54	27	
Progression-free survival at 24 weeks			0.001
No	41	9	
Yes	19	21	
Response			0.345*
Partial response or stable disease	7	6	
Progressive disease	53	24	

*Fisher's Exact Test.

11503 Oral Abstract Session

Camrelizumab plus apatinib in patients with advanced or refractory chordoma: A single-arm, open-label, phase 2 trial.

Cheng Yang, Qi Jia, Chenglong Zhao, Haifeng Wei, Tielong Liu, Xinghai Yang, Jian Jiao, Zhipeng Wu, Jian Zhao, Weiwei Zhou, Xiaomei Ma, Yan Lou, E Zhang, Jingyu Xing, Hao Zhang, Jianru Xiao; Department of Orthopedic Oncology, Changzheng Hospital, Navy Medical University, Shanghai, China; Department of Radiology, Changzheng Hospital, Navy Medical University, Shanghai, China

Background: The limited efficacy of current treatments for chordoma underscores the need for novel therapeutic options. Immune checkpoint inhibitors (ICI) have changed the landscape of cancer treatment but are rarely investigated for chordomas. Additionally, no established biomarkers reliably predict the efficacy of ICI and targeted therapies in this context. **Methods:** This investigator-initiated, single-arm, phase 2 trial evaluated the efficacy and safety of camrelizumab (anti-programmed death 1, PD-1) combined with apatinib (a tyrosine kinase inhibitor) in patients with advanced or refractory chordoma. Eligible patients received camrelizumab (200 mg intravenously every 2 weeks) and apatinib (250/500 mg orally daily) in 28-day cycles. The primary endpoint was objective response rate (ORR) assessed per RECIST 1.1 and Choi criteria. Secondary endpoints were median progression-free survival (PFS), overall survival, disease control rate (DCR) and safety. Next-generation sequencing (NGS) and fluorescence in situ hybridization (FISH) were used to explore predictive biomarkers. The trial is registered on Chictr.org.cn (ChiCTR2100042938). **Results:** Between September 2021, and October 2024, 38 patients were screened, and 33 were enrolled for efficacy and safety analyses. The median treatment duration was 7 months (IQR 4-14), with a median radiologic evaluation time of 10 months (IQR 9-13) and median follow-up of 15 months (IQR 9-22). At data cutoff, 15 (45.5%) patients remained on treatment. Per RECIST 1.1, seven patients (21.2%, [95% CI, 9.0-38.9]) achieved partial response (PR), with a 6-month DCR of 85.2% (23/27). The median PFS was 18.1 months (95% CI, 11.0-28.5). According to Choi criteria, 16 patients (48.5%, [95% CI, 30.8-66.5]) achieved PR, with a 6-month DCR of 77.7% (21/27) and a median PFS of 15.3 months (95% CI, 10.6-NE). Two patients died of tumor progression, and two others with cervical recurrent chordoma died from postoperative complications. NGS analyses revealed copy number deletion (CND) of CDKN2A in 30% (6/20) of cases. *Post hoc* FISH analysis of 25 specimens identified homozygous deletion (HD) of CDKN2A in 40.0% (10/25), which correlated with poorer outcomes. Adverse events (AEs) occurred in 93.9% (31/33) of patients, with grade 3/4 AEs in 48.5%. Treatment-related AEs led to apatinib dose interruptions in 39.4% and camrelizumab interruptions in 21.2%. **Conclusions:** The combination of camrelizumab and apatinib demonstrated promising efficacy and manageable toxicity in chordoma treatment. Furthermore, CDKN2A alterations (CND or HD) were associated with poorer outcomes, providing a potential biomarker for therapeutic stratification. Clinical trial information: ChiCTR2100042938. Research Sponsor: None.

11504 Oral Abstract Session

Off-label use of fam-trastuzumab deruxtecan in desmoplastic small round cell tumor.

Emily K Slotkin, Tamar Y. Feinberg, Umesh Bhanot, Anita Price, Gerald Behr, Neeta Pandit-Taskar, Narasimhan P. Agaram, Cristina R. Antonescu, Meera Hameed, Konstantinos Linos, Carla Saoud, Dylan Domenico, Elli Papaemmanuil, Filemon S. Dela Cruz, Chelsey Marie Burke, Michael Vincent Ortiz, Julia Lynne Glade Bender, Andrew Kung, Damon R. Reed; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Desmoplastic small round cell tumor (DSRCT) is a rare and aggressive sarcoma which remains almost universally fatal despite intensive, multi-modality therapy. Human epidermal growth factor receptor 2 (HER2) has been identified as a potential therapeutic target of relevance for DSRCT as both a pathway and cell surface expression marker. These observations prompted HER2 specific investigations in our DSRCT clinical cohort and subsequent off-label treatment with T-DXd, an antibody-drug conjugate consisting of a humanized anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor payload. **Methods:** A tumor microarray (TMA) of 52 unique DSRCT patient samples was analyzed by 2 immunohistochemical (IHC) assays (4B5, CB11), and a cohort of 61 DSRCT patient samples was analyzed by RNAseq. Additionally, 16 patients with relapsed/refractory DSRCT in need of therapy and enrolled on an institutional biobanking and genomic profiling protocol were identified, underwent IHC testing and RNAseq when feasible (fresh or archival tissue), and received off-label T-DXd. **Results:** TMA IHC analyses noted minimal HER2 IHC positivity using 4B5, with only 3/52 cases scoring above 10% membranous staining and composite IHC scores ranging from 11 to 15. IHC with clone CB11 uncovered 12.7-fold more HER2 reactivity with 38/52 cases scoring above 10%, and composite IHC scores ranging from 12.5 to 140. HER2 expression levels by RNAseq were analyzed in the context of 346 solid tumor patients with 22 histologies treated within the pediatrics department at MSK. Across these histologies DSRCT had the third highest HER2 expression level overall (surpassed only by papillary thyroid cancer and schwannoma). Median transcripts per million (TPM) expression level across the entire cohort was 9.8 (range 1-116.3), and for DSRCT was 41.8 (range 6.3-116.3). All 16 patients experienced clinical benefit (confirmed stable disease or partial response) with minimal toxicity, limited predominantly to myelosuppression, nausea and constipation. There were no episodes of interstitial lung disease. Notably, 8 of 16 patients all of whom had prior exposure to irinotecan achieved a decrease of at least 30% in the sum of the longest diameters of retrospectively selected target lesions, equivalent to a RECIST partial response (PR) (50% overall response rate). In this small series, response rate did not appear to correlate with available IHC or RNAseq data, with some patients achieving PR with no discernable membranous IHC expression. **Conclusions:** These results suggest that T-DXd is active in DSRCT and support the biomarker agnostic formal clinical trial which is planned with the Children's Oncology Group. Research Sponsor: Maurice Campbell Initiative at MSK KIDS; 76 Foundation; Will Heidrich Foundation.

11505 Oral Abstract Session

A phase I/II study of abemaciclib, a CDK4/6 inhibitor, in participants with HIV-associated and HIV-negative Kaposi sarcoma.

Ramya Ramaswami, Jose Mercado-Matos, Kathryn Lurain, Anaida Widell, Irene Ekwede, Ijeoma Agwu, Margaret Namubiru, Thomas A. Odeny, Crystal Lu, Denise Whitby, Robert Yarchoan; National Cancer Institute, Bethesda, MD; National Cancer Institute, National Institutes of Health, Bethesda, MD; Federick National Laboratory - Viral Oncology Section, Frederick, MD; HIV/AIDS Malignancy Branch, CCR, NCI, Bethesda, MD

Background: Kaposi sarcoma (KS), caused by Kaposi sarcoma herpesvirus (KSHV), is a multicentric angioproliferative tumor seen in people with and without HIV. Abemaciclib (abema) is an oral cyclin-dependent kinase (CDK) inhibitor that targets CDK4 (cyclin D1) and CDK6 (cyclin D3), and is FDA-approved for breast cancer. In vitro studies of KSHV-infected cells have shown that CDK4/6 inhibitors enhance host immune cell surface expression and T-cell activation induced by these cells. Here, we investigate the safety and activity of abema in participants (pts) with KS. **Methods:** In this open label, non-randomized, two-stage Phase I/II study of pts with KS, there were two primary objectives. Phase I evaluated the safety and tolerability of abema in pts with KS using a 3+3 dose de-escalation design to identify a maximum tolerated dose (MTD). The first group of pts were treated at dose level 1 (DL) of 200mg twice daily for days 1-28 of a 28-day cycle. Intra-participant dose reductions were permissible for abema-related toxicities. Phase II assessed the overall response rate of abemaciclib of all participants and stratified by prior systemic KS therapy (Arm 1 target: 15 pts with previously treated KS and Arm 2 target: 10 participants with untreated KS). Eligibility criteria included adherence to antiretroviral therapy in people with HIV (PWH) for $>$ 8 weeks prior to enrollment and no concomitant strong CYP3A4 inhibitors. KS response was evaluated using the modified AIDS Clinical Trials Group criteria. **Results:** Thirty-four pts (33 men) with a median age of 43 years were enrolled. Twenty-five (74%) were PWH and 27 pts had stage T1 KS (6 pts had either gastrointestinal and/or lung involvement). Among PWH, the baseline median HIV viral load was $<$20 copies/ml and the median CD4 T-cell count was 308 cells/μL (interquartile range: 176-468 cells/μl). In Phase I, 6 pts (4 PWH) were enrolled at 200mg BID with no dose-limiting toxicities. In Phase II, 17 pts (14 PWH) were enrolled to Arm 1, and 11 pts (7 PWH) enrolled to Arm 2. Overall, 3 pts (2 in Arm 1 and 1 in Arm 2) did not proceed after one cycle due to grade 2 anxiety in 2 pts and tremor in 1 pt that were unrelated to study therapy. These pts were replaced as KS response was not evaluable. The most common grade 1/2 adverse events were diarrhea (92%) and creatinine elevation (64%). Neutropenia of all grades was noted in 63% and 13 pts had dose reductions for recurrent grade 3 or grade 4 neutropenia. Among 31 evaluable pts receiving $>$2 cycles, 24 pts had a partial response (PR) (77% [95% confidence interval (CI): 59-90%]), 4 pts had stable disease and 2 pt had progressive disease. Sixteen of 21 pts who prior KS therapy had a PR (76% [95% CI: 53-92%]) and 8 of 10 pts in Arm 2 with previously untreated KS had a PR (80% [95% CI: 44-98%]). **Conclusions:** Abema is a novel therapeutic option in KS, with notable activity among pts with previously untreated KS. Adverse events were managed with dose reduction and supportive measures. Clinical trial information: NCT04941274. Research Sponsor: National Cancer Institute, Center for Cancer Research (Intramural Program).

11506 Oral Abstract Session

A randomized phase III trial of catequentinib hydrochloride (AL3818) versus placebo in subjects with metastatic or advanced leiomyosarcoma (LMS).

Robin Lewis Jones, Neal Shiv Chawla, Steven Attia, Seth Pollack, Lee D. Cranmer, Antonio Lopez-Pousa, Mahesh Seetharam, Melissa Amber Burgess, Bartosz Chmielowski, Brittany L. Siontis, Jonathan C. Trent, Breelyn A. Wilky, Nam Bui, Rashmi Chugh, Neeta Somaiah, Brian Andrew Van Tine, Sant P. Chawla; The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom; Sarcoma Oncology Center, Santa Monica, CA; Mayo Clinic Florida, Jacksonville, FL; Department of Medicine, Division of Hematology and Oncology, Northwestern University, Chicago, IL; University of Washington/Fred Hutchinson Cancer Consortium, Seattle, WA; Hospital de la Santa Creu i Sant Pau, Medical Oncology, Barcelona, Spain; Mayo Clinic Arizona, Scottsdale, AZ; University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA; University of California Los Angeles, Los Angeles, CA; Division of Medical Oncology, Mayo Clinic, Rochester, MN; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO; Division of Oncology, Department of Medicine, Stanford University, Stanford, CA; Michigan Medicine, Ann Arbor, MI; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Washington University in St. Louis, St. Louis, MO; Sarcoma Oncology Research Center, Santa Monica, CA

Background: Catequentinib Hydrochloride (AL3818, Anlotinib, Catequentinib) is a novel, orally administered, small molecule tyrosine kinase inhibitor. There remains an unmet need for effective, well tolerated therapies for patients (pts) with advanced/ metastatic leiomyosarcoma (LMS). We performed a randomized, double blind trial of Catequentinib monotherapy versus placebo in advanced/metastatic LMS. **Methods:** Patients with a diagnosis of LMS requiring third or further line treatment were eligible. Catequentinib was administered in a 21-day cycle with 14 days on and 7 days off regimen. In this double blind phase 3 trial, patients were randomized 2: 1 to Catequentinib or placebo, with the option of crossover to Catequentinib after confirmed Progression Disease (PD) on placebo. Progression-free survival (PFS) with Log Rank test was the primary endpoint and the trial was conducted at multiple sites in the US, UK and EU. **Results:** Total N = 111 patients were enrolled, and N = 110 were treated and evaluated, 74 randomized to Catequentinib (C), and 36 to placebo (P). In arms (C)/(P) median ages were 59.0/60.5 (range: 33-91) years respectively and 59/29 (79.7%/80.6%) were female. Median PFS by Blinded Independent Central Review (BICR) met the primary endpoint at 3.42 months (95% CI: 2.60, 6.83) for (C) and 1.41 months (95% CI: 1.35, 4.86) for (P) with a p-value of 0.0265 and a HR of 0.536 (95% CI: 0.307, 0.936). Median PFS for patients stratified at $\leq$ 3 prior lines was 4.86 months (95% CI: 2.04, 8.94) for (C) and 1.41 months (95% CI: 1.31, 4.86) for (P) with a p-value of 0.0046 and a HR of 0.386 (95% CI: 0.196, 0.760). The 6-month progression-free rate was 42.37% for (C) and 20.71% for (P). OS was 17.45 months (95% CI: 13.57, 19.32) for (C) and 16.33 months (95% CI: 11.27, NE) for crossover patients in the (P) arm. 30 (40.5%) of patients have experienced grade 3 treatment-related adverse events in the (C) arm compared to 3 (8.3%) of patients in the (P) arm. The most common TEAE for (C) vs (P) were diarrhea (50.0% vs 22.2%), stomatitis (31.1% vs 8.3%), fatigue (64.9% vs 41.7%), and hypertension (47.3% vs 19.4%). **Conclusions:** This phase 3 trial met the primary PFS endpoint and demonstrates superior PFS for Catequentinib vs placebo in metastatic/advanced LMS. This study confirms the acceptable benefit-risk profile of Catequentinib in LMS. Catequentinib is an effective and well tolerated treatment option for patients with LMS. Clinical trial information: NCT03016819. Research Sponsor: None.

11507 Oral Abstract Session

Alliance A092104: A randomized phase 2/3 study of olaparib plus temozolomide versus investigator's choice for the treatment of patients with advanced uterine leiomyosarcoma after progression on prior chemotherapy.

Brian Andrew Van Tine, Jacob B. Allred, Martee Leigh Hensley, Rebecca Christian Arend, John A. Charlson, Gina Z. D'Amato, Teresa Lee, Elizabeth Trice Loggers, Stephanie A. Berg, Matthew Ingham, Sumithra J. Mandrekar, Pamela N. Munster, Gary K. Schwartz; Washington University Siteman Cancer Center, St. Louis, MO; Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN; Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY; University of Alabama at Birmingham, Birmingham, AL; Medical College of Wisconsin, Milwaukee, WI; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Fox Chase Cancer Center, Temple University Hospital system, Philadelphia, PA; Clinical Research Division, Fred Hutchinson Cancer Center/Division of Hematology and Oncology, University of Washington, Seattle, WA; Alliance Protocol Operations Office, Chicago, IL; New York Presbyterian - Columbia, New York, NY; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Case Western Reserve University, Cleveland, OH

Background: Advanced uterine leiomyosarcoma (uLMS) is an aggressive malignancy with poor prognosis. Standard-of-care treatments, including trabectedin (Tb) or pazopanib (P), provide median progression-free survival (PFS) of 3-4 months (mo) and objective response rates (ORR) of ~11%. Homologous recombination deficiency (HRD) in a subset of uLMS supports the use of PARP inhibitors combined with DNA-damaging agents. Preclinical studies demonstrated synergistic activity of olaparib and temozolomide (T+O), and a prior single-arm Phase II study of T+O showed promising efficacy independent of an established biomarker, warranting further investigation in a randomized setting. **Methods:** Alliance A092104 is a Phase II/III trial evaluating olaparib (200 mg BID) plus temozolomide (75 mg/m^2 daily, days 1-7, every 21 days) versus investigator's choice of Tb or P in patients (pts) with advanced uLMS who progressed on ≥2 prior systemic therapies. Stratification factors included ECOG (0-1 vs. 2) and prior lines (2 vs. ≥3). The Phase II (Phase III) primary endpoint was PFS (OS), with a planned suspension of accrual at the end of Phase II. A total of 70 evaluable pts (58 PFS events) were needed to detect an improvement in PFS from 4 vs. 8 mo with power of 90% and 1-sided type I error of 10%, with futility assessed after 29 PFS events. Upon meeting the Phase II futility threshold for PFS, the trial was permanently closed. Data were released from the data and safety monitoring board. Pts continue to be followed for outcomes. **Results:** 74 pts enrolled (Arm 1: T+O, n = 37; Arm 2: investigator's choice, n = 37 (Tb, 18; P, 13; 6 pts did not start treatment). The arms were balanced for baseline demographics except race, with the T+O arm having a higher proportion of black/African American (29.7% vs. 16.2%). 21 pts remain on treatment. Hematologic adverse events (AEs) were more frequent in the T+O arm, with Grade 4 neutropenia (19.5%) and thrombocytopenia (8.3%) both managed by dose reductions. Non-hematologic Grade 3 AEs were higher in the investigator's choice arm (45.2% vs. 13.9%). No Grade 5 AEs were reported. In the first 70 pts, with a median follow-up of 5.9 mo, and 39 total PFS events, the median PFS was 3.2 mo (95% CI: 2.0-NE) for T+O versus 5.6 mo (95% CI: 2.8-NE) for investigator's choice (HR = 1.00; 95% CI: 0.60-2.17; 1-sided stratified log rank p = 0.50). Within Arm 2, the median PFS for Tb and P were respectively 5.6 (95% CI: 3.1-NE) and 3.8 (95% CI: 1.5-NE) mo. 3 pts in the T+O arm and 1 patient in the investigator's choice arm (Tb) had a confirmed partial response. **Conclusions:** The trial did not meet its primary endpoint of PFS in Phase II. This suggests that a biomarker may be needed before there is further exploration of PARP inhibitor-based regimens in uLMS. Overall survival and analysis of tissue-based biomarkers will be presented. Clinical trial information: NCT05432791. Research Sponsor: National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; National Cancer Institute; U10CA180820 (ECOG-ACRIN); National Cancer Institute; U10CA180868 (NRG Oncology).

11508 Oral Abstract Session

Spatial transcriptomic profiling from over 300 leiomyosarcoma samples.

Ryan A Denu, Zhao Zheng, Veena Kochat, Yingda Jiang, William Padron, Davis Ingram, Khalida M. Wani, Larissa Alejandra Meyer, Pamela T. Soliman, Ravin Ratan, Alexander J. Lazar, Emily Zhi-Yun Keung, Kunal Rai, Elise F Nassif Haddad; Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Leiomyosarcoma (LMS) is a smooth muscle-derived tumor with significant heterogeneity and limited treatment options for recurrent/metastatic disease. A lack of targetable driver mutations and prognostic and predictive biomarkers have hampered the care of patients with LMS. There is a great need to better understand the biology of LMS and develop novel therapeutics. Advances in single cell RNA sequencing (scRNA-seq) have allowed for better understanding of intratumoral heterogeneity in diverse cancer subtypes. However, tissue dissociation during this process leads to loss of spatial context. Spatial gene expression analysis builds upon scRNA-seq and has the potential to yield information about tissue organization, cell-cell interactions, niches, and cell states. To date there have been limited application of spatial transcriptomics to sarcoma. **Methods:** We performed single nucleus multiome (snRNA-seq and snATAC-seq) on a cohort of 16 primary, untreated LMS samples including 12 soft tissue (STLMS) and 4 uterine (ULMS) tumors. We then designed a custom 480-gene panel using the differentially expressed genes from clusters identified in snRNA-seq data to be able to identify spatial relationships between these clusters and to assess these clusters on a larger scale. We utilized the 10x Genomics Xenium platform. This was applied to LMS tissue microarrays (TMAs) comprising a total of 326 tissue cores from 127 unique patients. Matched primary and metastatic samples from the same patient were available for 33 patients. **Results:** Analysis of scRNAseq data identified 2 distinct subtypes: a dedifferentiated subtype with mesenchymal features (MES) and a differentiated subtype with enrichment of smooth muscle cell markers (SMC). Integration of chromatin accessibility data from snATACseq showed enrichment of nuclear factor I (NFI) transcription factor (TF) motifs in the MES and AP-1 motifs in the SMC group. Whole genome sequencing did not reveal an obvious genomic etiology for these subtypes. Spatial transcriptomics was able to identify these 2 subtypes in a larger cohort of tumors. Consistent with snRNAseq data, we find that most tumors had almost exclusively either MES or SMC cells. We assessed spatial relationships between these subtypes and infiltrating immune cells. This revealed an enrichment in immunosuppressive macrophages and exhausted T cells in MES tumors compared to SMC tumors. Analysis of matched primary and metastatic tumors demonstrated that the subtype (MES or SMC) generally remains consistent between different sites of disease. **Conclusions:** We identify 2 novel LMS subtypes (MES and SMC) driven by distinct TFs. Spatial transcriptomic analysis confirmed the presence of these 2 subtypes in a larger cohort and demonstrated that MES tumors are associated with a more immunosuppressive tumor microenvironment. Research Sponsor: None.

11509 Rapid Oral Abstract Session

Evaluation of the safety and efficacy of ALMB-0168, a novel monoclonal antibody activating Cx43 hemichannel, for osteosarcoma after standard therapy failure: A multicenter, open-label, single agent, phase 1/2 study (ACE study).

Jingnan Shen, Wei Guo, Jin Wang, Junqiang Yin, Xianbiao Xie, Lu Xie, Jie Xu, Xianan Li, Yong Zhou, Zhaoming Ye, Yang Dong, Chen Jing, Jianhua Lin, Guowen Wang, Weitao Yao, Yiying Bian, Xiugao Yang, Xuechao Wan, Shiwei Zhao, Yanfeng Zhang; Department of Musculoskeletal Oncology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; Peking University People's Hospital, Beijing, China; Musculoskeletal Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China; The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Department of Musculoskeletal Oncology Center, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; Peking University People's Hospital, Beijing, China; Hunan Cancer Hospital, Changsha, China; Department of Orthopedics, West China Hospital, Sichuan University, Chengdu, China; Department of Orthopedics, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; Department of Orthopedics, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Department of Orthopedic, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Henan Provincial Cancer Hospital, Zhengzhou, China; Department of Musculoskeletal Oncology Center, the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; CSPC Pharmaceutical Group Co., Ltd., Shijiazhuang, China; AlaMab, Phoenixville, PA

Background: There was limited therapeutic advancement for decades for patients (pts) with relapsed and refractory (R/R) osteosarcoma. Pts with R/R osteosarcoma urgently need effective and safe treatment options after standard therapy failure. ALMB-0168, a first-in-class humanized IgG4 monoclonal antibody targeted to hemichannel protein Cx43, activates hemichannels to release key substances including ATP into the extracellular environment, to inhibit the growth and migration of osteosarcoma and other cancers bone metastases. Here reported the phase 2 study result based on ASCO 2023 Poster (11530). **Methods:** Pts ≥ 12 years (yrs) with pathologically confirmed osteosarcoma who had failed standard therapy were enrolled. In the phase I dose escalation with an accelerated titration followed by 3+3 design, pts were dosed with 7 planned ALMB-0168 dose levels (1, 3, 6, 12, 18, 24, and 30mg/kg), Q3W, until their disease progressed or intolerable toxicity occurred. Then the cohort at effective dose 6mg/kg was expanded. This trial used RECIST1.1 for efficacy evaluation. Primary endpoints were safety and tolerability. Key secondary endpoints were overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). The CD73/CD39 expressions evaluated by IHC in osteosarcoma FFPE tissue with the efficacy were retrospectively analyzed. **Results:** As of Aug 19, 2024, total 27 pts with median age 29 yrs (range 16–69 yrs) were enrolled, of which 17 pts for dose escalation and 10 for dose expansion at 6mg/kg. No dose-limiting toxicity was observed. Treatment related adverse events (TRAEs) of any grade occurred in 18 (66.7%) pts, most of them were grade 1-2. Grade 3 TRAEs occurred in 1 (3.7%) patient (infectious pneumonia); no events were Grade 4 or 5. Common TRAEs observed in ≥ 10% pts were anemia (22.2%), proteinuria (14.8%) and alpha hydroxybutyrate dehydrogenase increased (11.1%). The DCR of whole evaluable pts was 68.2% (15/22), including 3 PR and 12 SD. At the 6mg/kg dose level which was expanded, among 10 evaluable pts, 2 pts achieved partial response (ORR: 20%), of which 1 patient achieved durable PR for 17 months (mo), PFS for 23 mo and OS for 36 mo (not reached). In 6mg/kg group, the DCR was 90% (9/10, 95% CI: 55.5, 99.7%) with 2 PR and 7 SD. And the PFS rate of 6mg/kg group at 4th mo was 70% (95% CI: 22.48, 91.83%). The relationship between the efficacy and the CD73/CD39 expression and other exploratory results will be presented in the future. **Conclusion:** The maximum tolerated dose of ALMB-0168 was not reached. The recommended phase 2 dose is 6mg/kg. In this study, ALMB-0168 showed encouraging anti-tumor activity, safe profile and durable benefit for pts with R/R osteosarcoma, which might be one of the potential treatment options for R/R osteosarcoma in the future. Clinical trial information: NCT04886765. Research Sponsor: AlaMab Therapeutics (Shanghai) Inc.

11510 Rapid Oral Abstract Session

Phase Ib trial of C019199, an oral TME modulator targeting CSF-1R/DDRs/VEGFR2, in relapsed or refractory osteosarcoma.

Feng Ye, Tian Gao, Lu Xie, Chaoyang Wu, Li Min, Kai Yang; The First Affiliated Hospital of Xiamen University, Xiamen, China; Department of Bone and Soft Tissue Tumor, Peking University Cancer Hospital, Beijing, China; Peking University People's Hospital, Beijing, China; The First Affiliated Hospital of Fujian Medical University, Zhenjiang, China; Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, China; The Second Hospital of Lanzhou University, Lanzhou, China

Background: C019199 is an oral drug candidate that modulates the tumor micro-environment (TME) through targeting CSF-1R/DDRs/VEGFR2. Previous phase Ia study of C019199 as a mono-therapy for advanced solid tumors has shown promising safety and anti-tumor activity. The osteosarcoma cohort of this Phase Ib study aims to further evaluate the safety and efficacy of C019199 in patients with relapsed or refractory osteosarcoma who had failed in the first-line chemotherapy. **Methods:** In this study, patients of ≥16 years and <76 years with histologically or cytologically confirmed osteosarcoma, progressing after at least one prior chemotherapy, were enrolled. The dosing regimen of C019199 is 200 mg once daily, with continuous administration over 21-day treatment cycles. Imaging assessments are performed every two cycles. The treatment continues until disease progression, intolerable toxicity, or withdrawal of informed consent by the patient. The primary endpoint is the incidence of adverse events (AEs) and serious adverse events (SAEs). Secondary endpoints include objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS). **Results:** A total of 30 patients with relapsed or refractory osteosarcoma were enrolled from October 2023 to November 2024. Median age was 29 years (range, 16–62), with 60% males. The most common treatment-related adverse events (TRAEs) were leukopenia (60%), increased creatine phosphokinase (53.3%), increased lactate dehydrogenase (53.3%), neutropenia (53.3%), thrombocytopenia (46.7%), diarrhea (43.3%), increased aspartate aminotransferase (43.3%), and lymphopenia (40.0%). Grade 3 or higher TRAEs were observed in merely 7 patients (23.3%) including neutropenia (3 pts), lymphopenia (2 pts), thrombocytopenia (1 pts), hypertension (1 pts), syncope (1 pts), and dyspnea (1 pts). One patient achieved a partial response (an ORR of 3.3%), while majority of patients achieved stable conditions with a DCR of 73.3%. Median PFS was 181 days, and the 3-month PFS rate was 66.7%. **Conclusions:** The data has demonstrated that C019199 exhibited a promising anti-tumor activity in patients of relapsed or refractory osteosarcoma. Combined with the encouraging tolerability and safety data, it suggests that C019199 has the potential to effectively benefit survival and improve quality of life for patients of this indication. The Phase Ib study is concluding, and a Phase III study is planned. Clinical trial information: CTR20202045. Research Sponsor: Fujian Haixi Pharmaceuticals Co., Ltd.

11511 Rapid Oral Abstract Session

Detecting ctDNA using personalized structural variants to forecast recurrence in localized soft tissue sarcoma (STS).

Changsu Lawrence Park, Elizabeth Demicco, Karen Howarth, Mitchell Elliott, Peter W. M. Chung, Miguel Alcaide Torres, Jasmine Lee, Nuria Segui, Limore Arones, Madeline J. Phillips, Völundur Hafstad, Peter Charles Ferguson, Samuel Woodhouse, Jay Wunder, David Benjamin Shultz, Abdulazeez Salawu, Albiruni Ryan Abdul Razak; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada; SAGA Dx, Morrisville, NC; Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Department of Surgical Oncology, Princess Margaret Cancer Centre and Department of Surgery, Mount Sinai Hospital, Toronto, ON, Canada

Background: The current standard for definitive management of localized STS involves surgery and (neo)adjuvant radiation (RT). Unfortunately, up to 50% of these patients (pts) recur but the role of adjuvant systemic therapy remains controversial. Circulating tumor DNA (ctDNA) is a promising biomarker for molecular residual disease (MRD) in STS but its clinical validity and utility remains unclear. Given that structural variants (SVs) are prevalent in the tumor genome of STS pts, this longitudinal study aims to utilize an ultra-sensitive, tumor-informed MRD assay that tracks somatic SVs for the detection of ctDNA. **Methods:** Pts with newly diagnosed, localized, high-risk ($\geq$ 5cm, grade $\geq$2) STS planned for curative-intent (neo)adjuvant RT and surgery were recruited from Feb 2019 to Aug 2023. Blood samples for ctDNA analyses were collected at diagnosis, post RT, post-surgery and every 3 months for up to two years in tandem with radiologic surveillance. The MRD window was defined as the first 8 weeks after surgery. Whole genome sequencing (WGS) was performed on archival tumor samples to detect all genomic SVs. A personalized multiplex digital PCR assay was then designed based on WGS data to track up to 16 somatic SVs in cell-free DNA from serial plasma samples for ctDNA detection and quantification. ctDNA data was then correlated to clinical outcomes (last updated on Jan 2025). **Results:** A total of 228 plasma samples from 32 pts were analyzed with a median follow-up of 20.1 months. STS subtypes included myxofibrosarcoma (12), undifferentiated pleomorphic sarcoma (10), dedifferentiated liposarcoma (6), pleomorphic liposarcoma (2), myxoid liposarcoma (1) and leiomyosarcoma (1). The ctDNA detection rate at diagnosis was 97% (31/32 pts). Of the cohort, 22 pts received preoperative RT and had blood collected within the MRD window. ctDNA was detectable at baseline and in the MRD window in 4/22 pts (18%). All 4 (100%) developed metastatic disease with a median lead time of 136 days (range: 28-210 days) in ctDNA detection prior to radiologic relapse. Of the 18 pts who were ctDNA-negative in the MRD window, 3 (17%) developed metastatic recurrence, all of which was preceded by detectable ctDNA with a median lead time of 87 days (range: 80-147 days). The median time from surgery to recurrence was 153 days (range: 57-224 days) vs 521 days (range: 406-631 days) for pts with detectable vs undetectable ctDNA within the MRD window, respectively. **Conclusions:** Detection of ctDNA using personalized tumor-informed assays for somatic SV tracking was feasible and highly sensitive in localized high-risk STS pts prior to surgery. Positive ctDNA within the MRD window was predictive of subsequent and earlier radiologic relapse. Based on this data, an interception trial of adjuvant systemic therapy for MRD-positive STS pts is planned. Future analysis, including the measurement of circulating extrachromosomal DNA (ecDNA) is planned. Clinical trial information: NCT03818412. Research Sponsor: None.

11512 Rapid Oral Abstract Session

A clinical and genomic landscape analysis of GI stromal tumors.

Nadeem Bilani, Sarah Orlando, Farres Obeidin, Akhil Chawla, Jeffrey D. Wayne, Pedro Viveiros; Department of Medicine, Division of Hematology and Oncology, Northwestern University, Chicago, IL; Università Campus Bio-medico Di Roma, Roma, Italy; Department of Pathology, Northwestern University, Chicago, IL; Department of Surgery, Division of Surgical Oncology, Northwestern University, Chicago, IL

Background: Gastrointestinal stromal tumors (GIST) are malignant mesenchymal tumors with distinct histogenesis and behavior from other sarcomas. Treatment of metastatic GIST involves receptor tyrosine kinase (RTK) inhibition. Primary *KIT* or *PDGFRA* mutations are established drivers of tumorigenesis via constitutive RTK activation. Growing attention is now focused on how secondary alterations impact clinical outcomes. **Methods:** The open-source platform cBioPortal was queried for GIST patients. Sociodemographic and clinicopathologic features, including *KIT*/*PDGFRA* mutation prevalence, were described using univariate statistics. Primary *KIT* mutations (exon 11: coding the receptor juxtamembrane domain) and secondary *KIT* mutations (exon 13/14: coding ATP-binding domain; or exon 17/18: coding activation loop) were assessed. Co-occurrence/exclusivity of altered genes was analyzed using two-sided Fisher's Exact (p-values) and Benjamini–Hochberg FDR correction (q-values) – pathway pairs deemed significant at $p < 0.05$ and $q < 0.05$. Log2 odds ratios (OR) quantified association strength. Differences between *KIT*-mutated (*KIT*-mut) vs. *KIT*-wild type (*KIT*-wt) groups were assessed via chi-squared. Kaplan-Meier modeling evaluated overall survival (OS) by co-occurring alterations, controlling for metastatic status and stratifying by primary site. **Results:** 499 GISTs were analyzed: 214 gastric (42.9%), 137 small bowel (27.5%), 22 colorectal (4.4%), and 9 esophageal (1.8%).Most tumors harbored *KIT* mutations (n = 382, 76.6%), which co-occurred with *CDKN2A* (log2 OR 3.04) and *CDKN2B* (log2 OR 2.77) deletions ($p < 0.001$; $q < 0.001$). 91 (23.8% of *KIT*-mut) patients harbored both (*CDKN2A/2B*-del). Secondary *KIT* mutations in exons 13/14 or 17/18 were associated with *CDKN2A/2B*-del ($p < 0.001$). *CDKN2A/2B*-del was rare in *KIT*-wt (< 5%). *KIT* mutations were mutually exclusive with *PDGFR, NF1* (log2 OR < -3, $q < 0.001$ for both), and *SDHA* mutations (log2 OR < -2.67, $q = 0.038$); prevalent in 9.8%, 4.0%, and 2.0%, respectively. *PDGFRA*/*NF1* mutations showed no significant co-occurrence. *SDHA* alterations were associated with *TERT* and *RICTOR* alterations. GISTs were more likely *KIT*-wt in women vs. men (OR 1.76, $p = 0.012$), and in gastric vs. small bowel tumors (OR 2.79, $p < 0.001$). Tumor mutational burden was similar between groups (mean 2.12 vs. 1.27). No tumors were microsatellite unstable.OS did not differ between *KIT*-, *PDGFRA*-, *NF1*-, or *SDHA*-mut (log-rank $p = 0.453$). In metastatic *KIT*-mut, *CDKN2A/2B*-del was associated with poorer OS (log-rank $p < 0.001$). Median OS for small bowel *KIT*-mut + *CDKN2A/2B*-wt disease was not reached, 24.3 months in small bowel *KIT*-mut + *CDKN2A/2B*-del, 52.5 in gastric *KIT*-mut + *CDKN2A/2B*-wt, and 22.4 in gastric *KIT*-mut + *CDKN2A/2B*-del. **Conclusions:** *CDKN2A*/*CDKN2B* deletions co-occur with advanced, imatinib-resistant, *KIT*-mut GIST. They prognosticate poorer OS but suggest therapeutic potential for cyclin dependent kinase inhibition. Research Sponsor: None.

11513 Rapid Oral Abstract Session

Phase II of sunitinib plus nivolumab in extraskeletal myxoid chondrosarcoma: Results from the GEIS, ISG, and UCL IMMUNOSARC II Study.

Nadia Hindi, Emanuela Palmerini, Irene Carrasco-Garcia, Enrique Gonzalezbilla, Claudia Valverde, Sandra J. Strauss, Toni Ibrahim, Ana Sebio, Robert Díaz-Beveridge, Javier Martínez-Trufero, Silvia Stacchiotti, Paola Collini, Roberto Tirabosco, Rafael Ramos, Antonio Gutierrez, David Silva Moura, Javier Martin Broto; Fundación Jimenez Diaz University Hospital, Madrid, Spain; University Hospital General de Villalba, Madrid, Spain; Instituto de Investigacion Sanitaria Fundacion Jimenez Diaz (IIS/FJD; UAM), Madrid, Spain; Osteoncologia, Sarcomi dell'Osso e dei Tessuti Molli, e Terapie Innovative - IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy; Hospital Universitario Virgen del Rocio, Seville, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain; Vall d'Hebron University Hospital, Barcelona, Spain; University College of London, London, United Kingdom; IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Hospital Universitario y Politécnico La Fe, Valencia, Spain; Instituto Aragonés de Investigación Sanitaria, Hospital Universitario Miguel Servet, Zaragoza, Spain; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Department of Advanced Diagnostics, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Royal National Orthopaedic Hospital, Stanmore, United Kingdom; University Hospital Son Espases, Mallorca, Spain; Hospital Universitario Son Espases, Palma, Spain; Health Research Institute-Fundación Jiménez Díaz University Hospital, Autonomous University of Madrid (IIS-FJD, UAM), Madrid, Spain; Fundación Jimenez Diaz University Hospital, Madrid, Spain

Background: Extraskeletal myxoid chondrosarcoma (EMC) is an ultra-rare sarcoma, with low sensitivity to classic chemotherapy. A previous clinical trial led by our groups showed the activity of antiangiogenics (specifically pazopanib) in patients (pts) with advanced ECM. As IMMUNOSARC I master-trial exploring sunitinib (S) plus nivolumab (N) in sarcoma detected signal of activity in ECM pts, a specific cohort of ECM was designed as a phase II trial within IMMUNOSARC II (NCT03277924). **Methods:** Adult pts with advanced, progressing, measurable and centrally confirmed EMC were enrolled and treated with S 37.5 mg/d in the first 14 days (d), followed by S 25 mg/d, along with N 240 mg every 2 weeks up to progression or intolerance. Imaging reassessments were done every 8 weeks. The primary endpoint was 6-month(m)-PFS rate, and the statistical assumptions were obtaining a 6m-PFSR in at least 15 pts out of 22 pts, with H_0= 50% and H_1= 80%, (α 0.05; β 0.10) to consider the combination as promising. **Results:** Twenty-four pts were accrued from May 2020 to July 2024 in 9 centres from Spain, Italy and UK. Pts had a median age of 58y (42-83), with a predominance of male (M = 19/F = 5). Thirteen (54%) pts were treatment naïve and 22 (92%) pts had metastatic disease at baseline. Grade 3-4 Adverse Events (AE) occurring in $>$ 5% of pts were: hypertension (29.2%), ALT and AST increase (16.7 and 12.5% respectively), bilirubin increase (12.5%), Lymphocytopenia (12.5%). No G4 hematologic AEs were found, with the exception of 1 pt with G4 leukopenia. With a median FU of 18 mos (8-29), among the 23 evaluable pts, 6m-PFSR was 77% with 16/23 pts free of progression at 6 mos, and a median PFS of 13.2 mos (95%CI 5.7-20.7). Median OS has not been reached and 12m-OS was 90% (95%CI 77-100). Two (9%) pts achieved a RECIST 1.1 partial response while 18 (82%) and 2 pts (9%) showed a stable disease and progresion as the best response respectively. Pts (6/23) previously treated with antiangiogenic had a trend to a shorter mPFS (7mos vs 13 mos, p = 0.11) and a significantly shorter OS (28 mos vs NR, p = 0.038). **Conclusions:** The combination of sunitinib and nivolumab has shown to be active in advanced extraskeletal myxoid chondrosarcoma. Our data suggest that using this combo in upfront lines provides a greater benefit. Clinical trial information: NCT03277924. Research Sponsor: Grupo Español de Investigación en Sarcomas (GEIS); Pfizer (drug supply); BMS (drug and shipping supply).

11514 Rapid Oral Abstract Session

ImmunoSarc2 (Cohort 7a): A Spanish Sarcoma Group (GEIS) phase Ib trial of epirubicin and ifosfamide plus nivolumab in first line of advanced undifferentiated pleomorphic sarcoma (UPS).

Javier Martin Broto, Javier Martínez-Trufero, Roberto Diaz Beveridge, Irene Carrasco-Garcia, David Silva Moura, Ana Sebio, Enrique Gonzalez-Billalabeitia, Rafael Ramos, Antonio Gutierrez, Josefina Cruz Jurado, Claudia Valverde, Patricio Ledesma, Nadia Hindi; Fundación Jimenez Diaz University Hospital, Madrid, Spain; Instituto Aragonés de Investigación Sanitaria, Hospital Universitario Miguel Servet, Zaragoza, Spain; Hospital La Fe, Valencia, Spain; Hospital Universitario Virgen del Rocio, Seville, Spain; Health Research Institute-Fundación Jiménez Díaz University Hospital, Autonomous University of Madrid (IIS-FJD, UAM), Madrid, Spain; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Department of Medical Oncology, Hospital 12 de Octubre, Madrid, Spain; Son Espases University Hospital, Palma De Mallorca, Spain; Hospital Universitario de Canarias; GEICAM Spanish Breast Cancer Group, Tenerife, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Vall d´Hebrón Institute of Oncology (VHIO), Barcelona, Spain; Sofpromed Clinical Research, Palma De Mallorca, Spain; Fundación Jimenez Diaz University Hospital, Madrid, Spain; University Hospital General de Villalba, Madrid, Spain; Instituto de Investigacion Sanitaria Fundacion Jimenez Diaz (IIS/FJD; UAM), Madrid, Spain

Background: It was hypothesized that anthracycline-based chemotherapy plus anti-PD1 (nivolumab) could enhance the activity of upfront chemotherapy in advanced UPS, based on a double-hit in the immunogenic cell death circuit. This peculiar tumor cell death eventually activates an adaptive immune response through particular molecular changes in dying tumor cells and microenvironment, triggered by specific drugs such as anthracyclines. We previously reported a phase Ib trial in leiomyosarcoma patients with the combination of doxorubicin, dacarbazine, and nivolumab, obtaining 56.5% of ORR. We present here the phase Ib, cohort 7a, of the ImmunoSarc2 trial. **Methods:** Adult patients (pts), with ECOG 0-1, naïve of previous anthracycline-containing treatments, and with a centrally confirmed diagnosis of advanced/metastatic UPS were eligible. Initial dose level 0 (L0) was defined as epirubicin 60 mg/m^2/d 20 min on D1 and D2 followed by ifosfamide 3 g/m^2/d 3-h on D1-3, plus nivolumab (NIV) 360 mg on D3 after chemotherapy. Cycles were given Q3W with GCSF and MESNA support. This combo would be given up to 6 courses of 21-day cycles, followed by 1-year NIV maintenance. A -1 dose level (L-1) was defined with the same regimen but with NIV 240 mg. A classic 3+3 phase 1 design was used to determine the MTD based on DLTs (main endpoint) observed during the first 21-day cycle. The cohort was foreseen to be extended with the RP2D to include up to a maximum of 20 evaluable patients. Secondary endpoints included ORR and safety profile among others. **Results:** Between January 2022 and June 2024, 16 patients M/F (9/7), ECOG 0/1 (15/1), with median age 56 years (29-77) were enrolled. All patients were treated with the initial L0 scheme and no DLTs were observed, being L0 the RP2D. Grade 3-4 toxicities were neutropenia 62.5%, febrile neutropenia 18.8%, anemia 31.3%, and thrombocytopenia 25%. A patient died following a subarachnoid hemorrhage in the context of grade 4 thrombocytopenia and an accidental fall. Of 16 patients, RECIST ORR according to local clinical site assessment was 68.8% distributed as 1 CR (6%), 10 PR (63 %), 4 SD (25%), and 1 PD (6%). With a median follow-up of 16.3 months (95% CI, 7.2-25.4), the median of PFS was 9.9 months (95% CI 7-12.7), while the median OS was not reached, and the 1-year OS rate was 81% (95% CI 62-100). **Conclusions:** Epirubicin 60 mg/m^2/d d1-2 plus Ifosfamide 3 g/m^2/d d1-3 plus NIV 360 mg on d3 Q3W, followed by 1 year of NIV is a feasible and manageable scheme that exhibits relevant activity as an upfront line in advanced UPS patients. A phase II/III trial is designed aiming to confirm the advantage of chemo-immunotherapy over chemotherapy alone in this context. Clinical trial information: NCT03277924. Research Sponsor: BMS provided budget for drug supply, shipping and some operational CRO cost; And Spanish Sarcoma Group (Sponsor).

11515 Rapid Oral Abstract Session

A phase 2 study using metronomic gemcitabine, doxorubicin, and docetaxel plus nivolumab in advanced leiomyosarcoma and liposarcoma (NCT04535713).

Jason Ballon, Princess "Angela" Savage, Anmol Dia Agarwal, Samantha Jeffrey, Sarosh Syed, Lauren Woolsey, Vanessa Xayasak, Stella Arakelyan, Ania M. Moradkhani, Victoria S. Chua-Alcala, Steve Wong, Doris V. Quon, Sant P. Chawla, Neal Shiv Chawla, Erlinda Maria Gordon; Sarcoma Oncology Center, Santa Monica, CA

Background: Chemotherapy agents cemcitabine, doxorubicin, and docetaxel have all demonstrated efficacy in soft tissue sarcomas (STS) but often result in significant toxicity. Therefore, we propose a combination chemo-immunotherapy regimen using metronomic low dose chemotherapy doses to reduce toxicity, with the addition of Nivolumab, a PD-1 inhibitor with demonstrated efficacy in STS. In this study, we aimed to determine the efficacy/safety of adding nivolumab to metronomic gemcitabine, doxorubicin, and docetaxel in subjects with advanced leiomyosarcoma (LMS) or liposarcoma (LPS). **Methods:** Objectives: Primary: To determine progression-free survival (PFS); Secondary: T evaluate the best overall response (BOR) and duration of response (DOR) by RECIST v1.1 via CT scan or MRI during the treatment period, determine progression-free survival rate (PFS) at 6 and 12 months and determine overall survival rate at 6 and 12 months Key eligibility criteria: $\geq$ 18 years, previously treated locally advanced unresectable or metastatic LMS/LPS, measurable disease by RECIST v1.1, acceptable hematologic and organ functions Treatment Schedule: Three-week treatment cycles with gemcitabine (600 mg/m2 max:1000 mg), doxorubicin (18 mg/m2; max: 32 mg), docetaxel (25 mg/m2; max:42 mg) on Day 1 and Day 8, andnivolumab (240 mg) on Day 1 only. **Results:** Efficacy: The intention-to-treat population (n= 41), which includes patients who received at least one dose of gemcitabine, doxorubicin, and docetaxel, was used to determine the following: Median OS =16.1 months (95% CI: 7.4 to 20.1 months) and incidence of adverse events. The modified-intention-to-treat population (n= 31), which includes patients who completed at least the first 2 treatment cycles and follow-up CT/MRI, was used to determine the following: Median PFS = 8.6 (95% CI: 3.3-12.0) months; ORR = 22.6%; DCR = 87.5%; 6-month PFS rate = 58%; 6-month OS rate = 70.7%; 12-month PFS rate = 35.5%; 12-month OS rate = 59.1%; BOR = 7 PR, 21 SD, 4 PD. Safety: 28 of 41 patients (68%) experienced Grade 3/4 TRAEs that include: thrombocytopenia (n=12), lymphocyte count decreased (n=11), anemia (n=10), neutropenia (n=9), back pain (n=4), leukopenia (n=4), fatigue (n=2), dyspnea (n=2), hypocalcemia (n=1), muscle weakness (n=1), colitis (n=1), diarrhea (n=1), anorexia (n=1), abdominal pain (n=1), alkaline phosphatase increased (n=1), nausea (n=1), bone pain (n=1), peripheral sensory neuropathy (n=1), edema (n=1). There were no unexpected adverse events. **Conclusions:** Taken together, the results indicate that the combination regimen of nivolumab with metronomic gemcitabine, doxorubicin and docetaxel may have synergistic activity and is an effective treatment for advanced leiomyosarcoma and liposarcoma with manageable toxicity. Clinical trial information: NCT04535713. Research Sponsor: None.

Subgroup analysis of the phase 2 part of the RINGSIDE phase 2/3 trial of varegacestat for treatment of desmoid tumors.

Rashmi Chugh, Mrinal M. Gounder, Arun S. Singh, Brian Andrew Van Tine, Vladimir Andelkovic, Janet Yoon, Edwin Choy, Jeremy Howard Lewin, Javier Martin Broto, Ravin Ratan, Nam Bui, Winette T.A. Van Der Graaf, Lara E. Davis, Atrayee Basu Mallick, Hyo Song Kim, Robin Lewis Jones, Eric Song, Katie Newhall, Jonathan Yovell, Bernd Kasper; University of Michigan, Michigan Medicine, Ann Arbor, MI; Memorial Sloan Kettering Cancer Center, New York, NY; University of California, Los Angeles, Santa Monica, CA; Washington University School of Medicine, St. Louis, MO; Princess Alexandra Hospital, Brisbane, Australia; City of Hope Comprehensive Cancer Center, Duarte, CA; Massachusetts General Hospital, Boston, MA; Peter MacCallum Cancer Centre, Melbourne, Australia; Fundación Jimenez Diaz University Hospital, Madrid, Spain; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Division of Oncology, Department of Medicine, Stanford University, Palo Alto, CA; Netherlands Cancer Institute, Amsterdam, Netherlands; Knight Cancer Institute, Oregon Health & Science University, Portland, OR; Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA; Yonsei University College of Medicine, Seoul, Reunion; The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom; Immunome, Bothell, WA; Immunome, Inc., Exton, PA; Mannheim University Medical Center, University of Heidelberg, Mannheim, Germany

Background: Gamma secretase inhibitors (GSIs) have shown antitumor activity against desmoid tumors (DT). The RINGSIDE Phase 2 study (NCT04871282) demonstrated early and continued response to three dose regimens of varegacestat (AL102) in patients with DTs. We evaluated treatment response in key subgroups. **Methods:** RINGSIDE Phase 2 is an open-label, dose-finding study in adults with progressing DT (≥10% unidimensional growth ≤18 months or DT-related pain requiring non-opioid medication). Participants were randomized to three dose regimens: 1.2 mg once daily (n=14), 2 mg intermittent (n=14) or 4 mg intermittent (n=14) (intermittent = 2 days on, 5 days off). In the open-label extension (OLE) period, all active participants began receiving 1.2 mg once daily. We performed descriptive analyses of objective response rate (ORR) in the following subgroups with at least 5 participants: age (≤40 years vs. >40 years), tumor size (<70 mm vs. ≥70 mm), prior lines of therapy (0, 1, or 2+), tumor location (intra-abdominal vs. extra-abdominal) and mutational biomarkers (*APC* vs *CTNNB1*). Subgroups were analyzed by pooling across dose regimens. **Results:** RINGSIDE Phase 2 enrolled 42 participants, of whom 29 (69%) entered the OLE. As of April 10, 2024, median time on treatment was 23.1 months (range 0.7 – 26.6) and 23 participants (55%) were still on treatment. Median age was 38.5 years (range 19 – 72), 74% were women, and 69% received prior DT therapy. ORR ranged from 43% to 78% across age, tumor size, prior therapy, tumor location and mutation subgroups (Table). Response rates were comparable across all subgroups examined. **Conclusions:** Comparable, objective tumor responses to oral varegacestat therapy were shown in all subgroups examined. These findings support continued evaluation of all desmoid tumor patients independent of subgroups in the ongoing, double-blind, randomized, placebo-controlled Phase 3 study of varegacestat (RINGSIDE NCT04871282). Clinical trial information: NCT04871282. Research Sponsor: Immunome.

Varegacestat response in subgroups.

Subgroups	ORR Responder (%)
Age ≤40 years (n=22) vs. >40 years (n=14)	13 (59) vs. 10 (71)
Tumor size <70 mm (n=18) vs. ≥70 mm (n=14)	13 (72) vs. 9 (64)
Prior lines of therapy: 0 (n=11), 1 (n=16), or 2+ (n=9)	6 (55), 10 (63), 7 (78)
Intra-abdominal (n=9) vs. extra-abdominal (n=27)	4 (44) vs. 19 (70)
***APC* (n=7) vs *CTNNB1* (n=19) mutation**	3 (43) vs. 13 (68)

11517 Rapid Oral Abstract Session

The broad-spectrum KIT inhibitor NB003 and activity in advanced gastrointestinal stromal tumors (GIST): Updated results from a phase 1 study (NCT04936178).

Ping Chi, Jian Li, Suzanne George, Michael C. Heinrich, Robin Lewis Jones, César Serrano, Min-Hee Ryu, Xinhua Zhang, Minggui Pan, Mehdi Brahmi, Haibo Qiu, Neeta Somaiah, Jiren Yu, Jun Zhang, Jung Yong Hong, Victor Moreno, Rastilav Bahleda, Kang Hu, Lijia Zhang; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Gastrointestinal Oncology, Laboratory of Carcinogenesis and Translational Research of the Ministry of Education, Peking University School of Oncology, Beijing Cancer Hospital & Institute, Beijing, China; Department of Medical Oncology, Sarcoma Center, Dana-Farber Cancer Institute, Boston, MA; Portland VA Health Care System and OHSU Knight Cancer Institute, Portland, OR; The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Department of Gastrointestinal Surgery, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; Sarcoma Program, Division of Oncology, Stanford University School of Medicine, Stanford, CA; Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France; State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, China; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, Chongqing, China; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; START-Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain; Gustave Roussy Cancer Campus, Department of Drug Development (DITEP), Villejuif, France; Ningbo Newbay Technology Development Co., Ltd, Shanghai, China; Ningbo Newbay Technology Development Co., Ltd., Shanghai, China

Background: NB003 is a novel potent and selective oral small-molecule tyrosine kinase inhibitor of KIT. It was designed to inhibit a broad spectrum of primary and acquired imatinib-resistant mutations in KIT. The abstract reports updated results from the escalation and expansion phases of the Phase 1 study in patients (pts) with advanced GIST. **Methods:** The Phase 1 study includes a dose-escalation phase where pts received oral NB003 (3mg to 40mg) twice daily (BID) in 28-day cycles, followed by an expansion phase with the putative recommended Phase 2 dose (RP2D) (15mg or 20mg BID) in 6 cohorts, including cohorts for GIST pts based on prior standard-of-care (SOC) regimens (2^{nd}, 3^{rd}, 4^{th}, and $\geq 5^{th}$-line). Efficacy was assessed by Modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 every 2 cycles. **Results:** At the cut-off of Dec 23, 2024, 158 pts with KIT-mutant GIST were enrolled in the escalation and expansion phases (median follow-up of 9.9 months; range, 0.5–32.0). The 154 evaluable pts included 24 2^{nd}-line, 30 3^{rd}-line, 35 4^{th}-line, 56 $\geq 5^{th}$-line pts and 9 others. The confirmed objective response rate (cORR) was 27.3% (95% CI:20.4, 35.0) in all, 40% (95% CI:22.7, 59.4) in 3^{rd}-line, 42.9% (95% CI: 26.3, 60.6) in 4^{th}-line, and 12.5% (95% CI:5.2, 24.1) in $\geq 5^{th}$-line pts. Tumor responses were observed in pts with a broad spectrum of acquired resistance mutations, including those in the KIT ATP-binding site (exons 13/14) and the activation loop of the kinase domain (exons 17/18). The median progression-free survival (mPFS) was 9.2 months (95% CI:7.4, 11.3), not reached (NR) (95% CI:6.0, NE), 13.8 months (95% CI:9.2, NE), and 4.5 months (95% CI:3.8, 7.4), in all, 3^{rd}-line, 4^{th}-line, and $\geq 5^{th}$-line pts, respectively. For $\geq 3^{rd}$-line pts without prior ripretinib, the cORR was 41.2% (95% CI:29.4, 53.8) and the mPFS was NR (95% CI:9.5, NE). In all pts, the most frequent treatment-related adverse events (TRAEs) were asymptomatic CPK increased (80.4%), anaemia (75.9%), AST increased (71.5%), face oedema (65.2%), periorbital oedema (55.1%), neutrophil count decreased (48.7%), WBC decreased (48.7%), amylase increased (39.9%), lipase increased (38.6%), platelet count decreased (33.5%), and peripheral oedema (31.0%). The most frequent treatment-emergent SAEs were anaemia (13.3%), gastrointestinal haemorrhage (6.3%), pleural effusion (4.4%), pneumonia (3.2%), and tumour haemorrhage (3.2%). **Conclusions:** NB003 demonstrated a manageable safety profile, and showed encouraging clinical benefit in GIST pts, as evidenced by mPFS and cORR, across multiple lines of treatment and a broad spectrum of secondary resistance KIT mutations. The promising data from this phase 1 study supports further testing of NB003 in Phase 3 studies. Clinical trial information: NCT04936178. Research Sponsor: None.

Liposomal irinotecan together with vincristine and temozolomide (NALIRI-VT) for patients with relapsed or refractory Ewing sarcoma: A two-cohort, phase 1a/1b study.

Jie Xu, Lu Xie, Xiaodong Tang, Xin Sun, Yiyang Yu, Weikang Wang; Peking University People's Hospital, Beijing, China

Background: To define the safety and preliminary efficacy of liposomal irinotecan together with vincristine and temozolomide in children and adults with Ewing sarcoma, respectively. **Methods:** Patients with relapsed or refractory Ewing sarcoma were enrolled in cohort A (children) or cohort B (adults), respectively. For each cohort, a fixed dose of vincristine (1.4mg/m^2 max 2mg i.v. $D_{1,8,15}$) and temozolomide (100mg/m^2/d p.o. D_{1-5}) q21d were given. In phase 1a portion, four dose levels of weekly infused liposomal irinotecan (level 1-4, 25mg/m^2, 30mg/m^2, 35mg/m^2 and 40mg/m^2) were designed. 3+3 dose-escalation method was used to explore the maximum tolerated dose (MTD), defined as no more than 30% patients appeared dose-limited toxicity (DLT) in first two cycles (six weeks). In the phase 1b portion, MTD would be used and a maximum of 12 patients were allowed in each cohort at this level in total. **Results:** 15 children and 18 adults were enrolled in phase 1a portion. 9 more children and 5 more adults were enrolled in phase 1b portion. Finally, 12 children and 11 adults were treated at MTD level. In phase 1a portion, no DLT was found at level 1-2. For level 3, no DLT (0/3) was found in cohort A, while one DLT (1/6) of hematologic toxicity was found in cohort B. For level 4, two DLTs (2/6) were found in cohort A, both of whom were due to hematologic toxicity. For cohort B, two DLTs (2/6) was found at this level. One of them was serious anorexia. The other one was hematologic toxicity together with serious nausea and vomiting, anorexia, fatigue. Level 3 was chosen for MTD. Grade 3/4 toxicities were found in hematologic toxicity (most common), anorexia, fatigue, nausea or vomiting, pain and diarrhea. Better efficacy was shown at higher levels (level 3 and level 4) in both cohorts. For cohort A, objective response rate (ORR) was 0 (0/3), 33.3% (1/3), 66.7% (2/3) and 66.7% (4/6) at level 1-4, respectively. For cohort B, ORR was 33.3% (1/3), 33.3% (1/3), 83.3% (5/6) and 66.7% (4/6). Data for survival in phase 1a and data of phase 1b were not matured. **Conclusions:** We showed that liposomal irinotecan infused weekly at 35mg/m^2 in NALIRI-VT regimen was well tolerated and showed promising efficacy in both children and adults. Clinical trial information: NCT06340204. Research Sponsor: Beijing Tongzhou technology grand; KJ2024CX046.

Summary of DLTs and responses in phase 1a portion.

Dose level	Liposomal Irinotecan IV Dose (mg/m^2/d) $D_{1,8,15}$	# of Evaluable Patients	# of DLTs in the first two cycles	Best of Response (BOR)
Cohort A Children				
1	25	3	0	1 SD, 2 PD
2	30	3	0	1 PR, 1 SD, 1 PD
3	35	3	0	1 CR, 1 PR, 1 SD
4	40	6	2	1 CR, 3 PR, 2 PD
Cohort B Adults				
1	25	3	0	1 SD->CR*, 2 SD
2	30	3	0	1 PR, 2 SD
3	35	6	1	5 PR, 1 PD
4	40	6	2	1 CR, 3 PR, 2 SD

*One patient was first treated at level 1, showed no AE at this level and SD was recorded at first evaluation. When safety of the next level 2 dose was confirmed, this patient received the higher level 2 dose, and CR was recorded at the following evaluations.

11519 Poster Session

MRI-based machine learning model for predicting early relapse in osteosarcoma following neoadjuvant chemotherapy.

Yucheng Fu, Qi Liu, Zhusheng Zhang, Le Qin, Weibin Zhang; Department of Orthopedics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, Shanghai, China; Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Early relapse (ER, ≤ 1 year) in osteosarcoma frequently occurs following neoadjuvant chemotherapy (NAC) and surgical resection. This study developed the machine learning models integrating radiomics, clinical, and pathological features to predict ER risk in osteosarcoma. **Methods:** 142 osteosarcoma patients were retrospectively analyzed and preoperative MRI images (T1- and FST2-weighted) were obtained after NAC. After feature extraction and selection, 5 machine learning classifiers—random forest (RF), support vector machine, logistic regression, decision tree, and gradient boosting tree—were implemented to construct radiomics, clinicopathological, and multimodal models. The performance of these models were assessed and compared using receiver operating characteristic curves, decision curve analysis (DCA), and Kaplan-Meier survival analysis, with the components and structure of the best-performing model subsequently visualized. **Results:** The RF algorithm outperformed the other classifiers, forming optimal radiomics and multimodal models. The RF-based multimodal model, combining 14 radiomics features, alkaline phosphatase (ALP) levels, and tumor necrosis rate, achieved the highest performance, with an area under the curve (AUC) of 0.978 in the training cohort and 0.913 in the testing cohort. The corresponding radiomics model, designed for real-time preoperative evaluation, showed a slight reduction in performance but still performed well. DCA and Kaplan-Meier curves indicated significant clinical utility of these two models. **Conclusions:** The RF-based pipeline, which includes radiomics and multimodal models, could facilitate personalized chemotherapy by identifying high-risk patients, optimizing treatment decisions, and improving outcomes. Research Sponsor: National Natural Science Foundation of China; 82472712.

Performance of the different radiomics models, clinical models and combined models in the training and testing cohorts.

Cohorts	Model	Classifier	AUC (95% CI)
Training cohort	Radiomics models	RF	0.963 (0.928-0.998)
		SVM	0.811 (0.723-0.899)
		LR	0.802 (0.714-0.891)
		DT	0.876 (0.809-0.942)
		GBT	0.973 (0.942-0.999)
	Clinical models	LR	0.709 (0.614-0.803)
	Combined models	RF	0.978 (0.956-0.999)
		SVM	0.898 (0.836-0.960)
		LR	0.813 (0.728-0.898)
		DT	0.896 (0.834-0.958)
		GBT	0.931 (0.884-0.977)
Testing cohort	Radiomics models	RF	0.857 (0.751-0.963)
		SVM	0.784 (0.650-0.917)
		LR	0.794 (0.662-0.927)
		DT	0.814 (0.686-0.942)
		GBT	0.728 (0.561-0.896)
	Clinical models	LR	0.684 (0.525-0.843)
	Combined models	RF	0.913 (0.833-0.994)
		SVM	0.818 (0.671-0.965)
		LR	0.812 (0.659-0.965)
		DT	0.881 (0.773-0.989)
		GBT	0.853 (0.731-0.974)

RF: Random forest; SVM: Support vector machine; LR: Logistic regression; DT: Decision tree; GBT: Gradient Boosting Tree; CI: Confidence interval.

11520 Poster Session

The preoperative management of patients with giant cell tumors in limb bones using denosumab therapy.

Saidrasul Nasirov, Djamila Polatova, Khurshid Abdikarimov, Nargiza Karimova, Rasulbek Davletov, Alexander Savkin, Bahridil Sultonov, Nuriddin Kamolovich Asamedinov, Abbos Nurjabov, Oybek Abdusattorov; Tashkent Medical Academy, Tashkent, Uzbekistan; Center of Pediatric Hematology, Oncology and Clinical Immunology, Tashkent, Uzbekistan; Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan; Tashkent State Dental Institute, Tashkent, Uzbekistan

Background: Giant cell tumor (GCT) is an intermediate, locally aggressive primary bone tumor. In addition to local therapy,new drugs for the treatment of this disease have become available. The medication Denosumab, which wasoriginally used to treat osteoporosis and the solid tumor metastases to bone, eventually began to be used totreat giant cell bone tumors. In treatment of GCT, Denosumab was used as the only remedy in patients withinoperable tumors, and was also used before surgery to reduce the size of the tumor and to preserve the joint.To evaluate the effectiveness of Denosumab, while using in the preoperative period of GCT treatment. **Methods:** A study was conducted of 49 patients with GCT of tubular limb bones who received Denosumab beforesurgery, and 60 patients (retrospectively evaluated, without using Denosumab in our hospital from 2015 to2019). Propensity scores were compared in a 1:1 ratio between the groups receiving Denosumab and thecontrol group to minimize possible selection bias; recurrence rates, limb function, and surgical impairmentwere compared between the two groups. **Results:** The recurrence rate after 3 years in the Denosumab group and the control group was 12.2% and 23.3%,respectively. In the Denosumab group, 100% (n = 49) of patients underwent surgical treatment. In 44 patientstreated with Denosumab, the indices of limb joint preservation were 89.8% and 36.6% in 22 control patients.Postoperative MSTS were higher in patients in the Denosumab group than in the control group. **Conclusions:** Preoperative treatment with Denosumab reduced the risk of local recurrence of GCT. Preoperative treatmentwith Denosumab is indicated for patients with advanced GCT to facilitate surgical treatment and preserve thejoint. Denosumab remains a highly effective treatment for patients with GCT bone. Research Sponsor: None.

11521 Poster Session

Feasibility and clinical outcomes of imatinib personalized dosing in gastrointestinal stromal tumor patients.

Maud Berendina Annelies van der Kleij, Eline Giraud, Niels A.D. Guchelaar, Kim Westerdijk, Marinda Meertens, Martijn Koolen, Roos F. Bleckman, Hans-Martin M.B. Otten, Helle-Brit Fiebrich, Stijn L.W. Koolen, Hans Gelderblom, Dirk Jan A.R. Moes, An K.L. Reyners, Daan J. Touw, Ron H.J. Mathijssen, Nielka P. Van Erp, Ingrid M.E. Desar, Alwin Huitema, Neeltje Steeghs, Dutch Pharmacology Oncology Group; Department of Clinical Pharmacology, Division of Medical Oncology, Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, Netherlands; Department of Pharmacy, Radboud University Medical Center, Nijmegen, Netherlands; Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands; Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands; Department of Pharmacy & Pharmacology, Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, Netherlands; Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands; Department of Medical Oncology, Meander Medical Center, Amersfoort, Netherlands; Department of Medical Oncology, Isala Clinics, Zwolle, Netherlands; Leiden University Medical Center, Leiden, Netherlands; Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, Netherlands; Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Netherlands Cancer Institute, University Medical Center Utrecht, Utrecht, Netherlands

Background: Imatinib treatment for metastatic gastrointestinal stromal tumors (GISTs) has substantial overall survival benefits compared to chemotherapy (56 vs 9 months) (Balachandran, 2014). Even better outcomes have been demonstrated for patients with imatinib minimal drug concentrations (C_{min}) $\geq$ 1100 ng/mL (Demetri, 2009). Drug concentration-guided dosing through therapeutic drug monitoring (TDM) of imatinib has previously been described as an option for personalized dosing, but there is no definite conclusion on efficacy results (IJzerman, 2020). The aim of the current study was to evaluate the feasibility and effect on clinical outcomes of imatinib personalized dosing through TDM for GIST patients. **Methods:** GIST patients starting with imatinib 400 mg once daily (QD) in both the (neo)adjuvant and metastatic setting were included. C_{min} levels were measured during routine outpatient clinic visits, at 4, 8 and 12 weeks after start of treatment, and every 12 weeks thereafter. Dose increase to 600 mg QD and, if necessary, to 800 mg QD was advised when $C_{min} < 1100$ ng/mL and treatment was well tolerated. Dose interventions were considered successful when median C_{min} was $\geq$ 1100 ng/mL after intervention and no dose limiting toxicities (DLTs) occurred within the first month after dose intervention. **Results:** A total of 171 GIST patients were included, of which 61% (n = 104) were treated in the (neo)adjuvant setting and 39% (n = 67) in the palliative setting. Most patients (85.4%, n = 146) had a *KIT* exon 11 mutation. Median time on treatment was 30 months. A total of 1475 C_{min} levels were measured (median of 8 levels per patient, IQR: 4–12), resulting in a median C_{min} of 1111 ng/mL. Among all patients, 16% (n = 27) had all adequate C_{min} levels, and 84% (n = 144) had $\geq$ 1 C_{min} level below the target. Of these, 60% (n = 87) had a dose intervention, which was successful in 76% (n = 66) and unsuccessful in 24% (n = 21) of patients. When dose interventions were unsuccessful, this was primarily because C_{min} levels were still below the target after the intervention (62%, n = 13). In the 40% of patients (n = 57) with $\geq$1 C_{min} level below the target who had no dose intervention, this was mostly due to DLTs (51%, n = 29). Median C_{min} before the dose intervention was 953 ng/mL, which increased to 1200 ng/mL ($p < 0.001$) after the intervention. DLTs were not correlated with dose interventions ($p = 0.13$; OR: 1.86, 95% CI: 0.83–4.16). **Conclusions:** This study confirms that personalized dosing of imatinib through TDM in GIST patients is feasible. Adequate drug concentrations improved from 16% to 54% of patients and interventions resulted in a clinically relevant drug concentration increase in patients who previously had C_{min} levels below the target. Comparison of treatment efficacy and toxicity in our cohort with a standard-dose historical cohort will elucidate the effect of personalized dosing through TDM on clinical outcomes (analyses ready before ASCO). Clinical trial information: NTR6866 — AND project number 11575. Research Sponsor: Ipsen; NA; GSK; NA; Novartis; NA; Pfizer; NA; Roche; NA; Dutch Cancer Society (KWF Kankerbestrijding); 11575.

11522 Poster Session

Personalized tumor-informed circulating tumor DNA analysis in monitoring recurrence following resection of high-risk locally advanced stage gastrointestinal stromal tumor.

Zhidong Gao, Baosen Cheng, Shuya Yang, Yudi Bao, Peng Cui, Chengcheng Li, Fujun Qiu, Guoqiang Wang, Shangli Cai, Xin Wu, Dongbing Zhao, Zhaodong Xing, Feng Cao, Wei Zhang, Yingjiang Ye; Peking University People's Hospital, Beijing, China; Peking University People`s Hospital, Beijing, China; Burning Rock Biotech, Guangzhou, China; Burning Rock Biotech, Shanghai, China; Chinese People's Liberation Army General Hospital, Beijing, China; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Xuanwu Hospital of Capital Medical University, Beijing, China

Background: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. Radical resection is the standard treatment of localized GIST, yet the 5-year recurrence rate for high-risk GIST is more than 50%. It remains unclear whether detecting post-surgery molecular residual disease (MRD) via circulating tumor DNA (ctDNA) can predict the recurrence of high-risk locally advanced GIST. **Methods:** Patients with high-risk locally advanced stage GIST who underwent R0 surgery were enrolled prospectively. Surgical tissue samples were collected. Blood samples were collected pre-surgery, within 1-month post-surgery, and every 3–6 months thereafter. Tumor-derived variants were identified by whole-exon sequencing of the surgical tissues. Up to 50 highly ranked variants with allele frequency 3.0% were selected for the personalized panel design, which was subsequently used to assess MRD status. **Results:** As date cutoff of December 2024, 44 eligible patients were enrolled, among whom 42 tissue samples, 41 pre- and 166 post-surgical blood samples were collected and analyzed, and the median follow-up time was 21 months. Tissue-based sequencing identified variants in *KIT* and *PDGFRA* in 37 (84.1%) and 4 (9.1%) patients, respectively. Positive MRD was detected in 56.1% (23/41) of all pre-surgical plasma samples. Pre-surgical MRD positivity was associated with tumor volume, mitoses and Ki-67 ($P < 0.05$). Landmark analysis within 1 month post-surgery showed that 4 patients (4/41, 9.8%) were positive for ctDNA. Patients with positive MRD at landmark showed marginally worse DFS compared with those with negative MRD (HR = 4.24, 95% CI = 0.81-22.26, P = 0.07).To date, 7 patients have been detected recurrence by CT scan. Among the 4 patients with both radiological and MRD positivity, longitudinal ctDNA detected recurrence with lead-time of 3 months compared with CT scan for 2 patients. The other 2 cases are simultaneously. Notably, these 4 patients didn't receive regular adjuvant therapy. Furthermore, the longitudinal MRD positivity was associated with inferior DFS after adjusting sex, age, TNM stages and whether receiving adjuvant therapy in the multivariable cox regression (HR = 5.63, 95% CI = 1.09-28.99, P = 0.04). Additionally, 30 patients with consistent negative MRD during surveillance exerted significantly superior survival compared with patients whose MRD status converted to negative (n = 2), converted positive (n = 7) and remained consistently positive (n = 2) from landmark to longitudinal monitoring (P = 0.04). **Conclusions:** The present study suggests that personalized tumor-informed ctDNA has the potential to inform recurrence in high-risk locally advanced stage GIST patients, especially for patients who have not received regular adjuvant therapy. Clinical enrollment is still ongoing. Clinical trial information: NCT05408897. Research Sponsor: Beijing Bethune Charitable Foundation; Research and Development Fund of Peking University People's Hospital.

11523 Poster Session

The benefit of cytoreductive surgery during imatinib (IM) therapy in patients with metastatic gastrointestinal stromal tumors (mGISTs): Retrospective analysis from several cancer centers.

Daria Filonenko, Ramiz Valiev, Maksat Nurberdiyev, Peter Arkhiri, Maxim P. Nikulin, Lyudmila Zhukova, Igor Khatkov; SBIH Moscow Clinical Scientific and Practical Center Named After A.S. Loginov of DHM, Moscow, Russian Federation; N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation

Background: the role of cytoreductive surgery for patients with mGISTs during IM therapy has not been established yet because the absence of randomized trials. We carried out a retrospective analysis of the outcome of patients with mGISTs in several Moscow cancer centers. **Methods:** we compared several cohorts: treated with IM only (IM group) and treated with IM and surgery, the latter was divided into four groups depending on the time of the surgery and the response to IM: before IM (BIM), after partial response or stable disease (RD), or unifocal progressive disease (UPD) or multifocal progressive disease (MPD). Patients received IM after surgery until progression. The primary end points were progression free survival and overall survival from the start of IM therapy. **Results:** 234pts with mGISTs from 2002 till 2024 received IM 400 in the first line. 116 pts received imatinib only, 118 patients underwent cytoreductive surgery: before IM (BIM, n=39) and during IM – on responsive disease (RD, n=23), unifocal progressive disease (UPD, n=22), and multifocal progressive disease (MPD, n=27). 7 patients were excluded from the analysis because they underwent surgery twice (before and during IM). Cytoreductive surgery increased the median PFS in comparison with IM only (Table). The differences were statistically significant between IM vs BIM – 24.0 vs 61.0 (p=0.028), IM vs RD – 24.0 vs 77.0 (p=0.003), and RD vs MPD – 77.0 vs 39.0 (p=0.005). Patients with UPD and MDP had a median PFS after R0/R1 and R2 was 17.0 vs 7.0 (p=0.564) and 14.0 vs 7.0 (p=0.056) months, respectively. Patient who underwent surgery on progression received IM after surgery for 10.0 and 11.0 months in UPD and MPD groups respectively what was two times longer than on sunitinib therapy (the median PFS 6.8 months, NCT00075218). On multivariate analysis for the entire cohort radiologic response was predictive for PFS: RD (hazard ratio (HR) 0.37, p = 0.003), UPD (HR 0.47, p=0.03) and BIM (HR 0.48, P = 0.009) were independent prognostic factors of better PFS; *KIT* exon 9 mutations (HR 2.68, p=0.003) and unknown location of primary tumor – factors of worse PFS. Overall survival was reached only in MPD group – 75.0 (95% CI: 37.14-112.87) months from the start of IM. **Conclusions:** cytoreductive surgery during IM therapy in responsive disease increase PFS; metastasectomy on UPD is likely to be beneficial for patients with mGISTs and it can be more effective option than the second line treatment. Research Sponsor: None.

			95% CI	
	PFS, median, months	Standard error	Lower bound	Upper bound
IM only (n=116)	24.000	4.459	15.260	32.740
Surgery before IM (n=39)	61.000	28.061	6.001	115.999
RD (n=23)	77.000	21.954	33.971	120.029
UPD (n=22)	70.000	25,077	20.849	119.151
MPD (n=27)	39.000	5.747	27.736	50.264

11524 Poster Session

In vitro profiling of IDRX-42 against secondary and tertiary mutations (AP/AL) found in TKI-resistant GIST.

Michael C. Heinrich, Ajia Town, Marcelina Roberti, Thomas Mühlenberg, Sebastian Bauer; Portland VA Health Care System and OHSU Knight Cancer Institute, Portland, OR; West German Cancer Center, Sarcoma Center, University Clinic Essen, Essen, Germany; Department of Medical Oncology, Sarcoma Center/West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany

Background: The majority of Gastrointestinal Stromal Tumors (GIST) harbor a KIT mutation and respond to imatinib (IM), but over time clinical resistance emerges due to secondary mutations. These secondary mutations are restricted to two regions of the KIT protein: the drug/ATP binding pocket (AP, exons 13 and 14) and the activation loop (AL, exons 17 and 18). Although additional TKI drugs has been approved for later lines of therapy, these agents lack activity against the entire spectrum of known secondary resistance mutations. For example, sunitinib is potent against AP mutations (V654A, T670I), but has minimal activity against AL mutations. Recently, IDRX-42 has demonstrated promising activity in a phase 1/1b study of patients with TKI-resistant GIST. However, the cellular potency of IDRX-42 against various primary, secondary, and compound AP/AL KIT mutations has not been comprehensively described. **Methods:** We used a panel of GIST cell lines with various mutations that were derived from the parental GIST T1 cell line (primary KIT exon 11 (K11) deletion mutation). We also transiently expressed additional mutations in CHO cells. Densitometry and curve fitting was used to determine the biochemical IC50 for inhibition of KIT autophosphorylation, an accepted surrogate for KIT kinase activity. We also profiled IM and ripretinib (RIP) in the same cell line models. **Results:** IM was active against primary K11 mutations but was much less active against K11 + AP, K11 + AL, KIT exon 9 (K9), K9 + AP, and K9 + AL mutations. In addition, IM was inactive against K9 or K11 + AP/AL mutations (with all three mutations in cis). RIP potently inhibited K11, K11 + AL mutations, and K9 + AL mutations. However, RIP was less active against K11 + AP, K9 +AP, and K9 or K11 + AP/AL mutations. IDRX-42 was active against K11, K11 + V654A, K11 + AL, K9, K9 + V654A, and K9 +AL mutations. However, IDRX-42 lacked potency against the gatekeeper T670I (AP) mutation and K9 or K11 + AP/AL mutations. We developed resistant cell lines using GIST T1 cell line subjected to chemical mutagenesis and long-term drug selection with IDRX-42. All IDRX-42 resistant clones had an acquired T670I mutation, but no other secondary mutations were identified. **Conclusions:** IDRX-42 has superior biochemical potency against a panel of primary and secondary KIT mutations compared with IM or RIP. Additionally, IDRX-42 has activity against K9 or K11 + V654A, and K9 or K11 + AL; However, K9 or K11 with T670I mutant kinases were resistant. Notably, none of these three profiled drugs had activity against K9 or K11 + AP/AL mutations. The optimal clinical use of IDRX-42 may be in earlier lines of therapy, prior to the emergence of AP/AL mutations. Research Sponsor: None.

Biochemical IC50 for inhibition of KIT autophosphorylation.

Cells	Mutation	IDRX-42 (nM)	IM (nM)	RIP (nM)
GIST T1	K11	S	S	S
GIST T1	K11 + V654A	S	R	R
GIST T1	K11 + T670I	R	R	R
GIST T1	K11 + AL	S	R	S
CHO	K9	S	R	S
CHO	K9 + V654A	S	R	R
CHO	K9 + T670I	R	R	R
CHO	K9 + AL	S	R	S
CHO	(K9 or K11) + AP/AL	R	R	R

11525 Poster Session

15-year survivorship in patients with metastatic gastrointestinal stromal tumors.

Julia A. Levy, Thomas L. Sutton, Skye C. Mayo, Michael C. Heinrich; Department of Internal Medicine, Oregon Health & Science University, Portland, OR; Cedars Sinai Medical Center, Department of Surgery, Los Angeles, CA; OHSU Knight Cancer Institute, Portland, OR; Oregon Health & Science University, Knight Cancer Institute, Portland, OR

Background: Prior studies of metastatic gastrointestinal stromal tumors (mGIST) have largely focused on 5-year survival when evaluating long-term outcomes, but factors underlying longer-term survival remain less understood. This retrospective study aimed to identify factors associated with 15-year survivorship in patients with mGIST. **Methods:** Patients with mGIST treated at Oregon Health & Science University between 2003-2023 were identified from the Knight Cancer Registry. Data were abstracted through manual chart review. Patients were categorized into two cohorts: those who died before 15 years of follow-up, and those who survived ≥15 years following mGIST diagnosis. Chi-square and independent samples t-tests were performed to compare clinicopathologic variables between the two groups. **Results:** Of the 111 eligible patients (66 male [59.5%]; 45 female [40.5%]; median [IQR] age, 57 [46-71] years, 88.3% Non-Hispanic White), nineteen (17.1%) survived ≥15 years after mGIST diagnosis. Factors associated with 15-year survival were younger age at metastatic diagnosis (44 [32-56] vs. 60 [53-73], p<0.001) and metastasectomy (n=12 [63.2%] vs. 27 [29.3%], p=0.008). Most (68.4%) patients who underwent metastasectomy did so before they developed resistance to imatinib. Patients who underwent metastasectomy before developing resistance were more likely to achieve 15-year survival, however, this association was not observed in those who underwent metastasectomy after imatinib resistance. Patients who underwent metastasectomy also experienced a longer median time to imatinib resistance relative to those who did not (55 months vs. 23 months, p=0.001). **Conclusions:** This retrospective study supports that younger age at metastatic diagnosis and metastasectomy before the development of imatinib resistance are factors associated with 15-year survivorship in patients with mGISTs. These findings suggest that surgical resection of metastases in select patients may prolong the duration of imatinib response and potentially improve long-term outcomes. Research Sponsor: None.

Tumor and treatment factors associated with 15-year survivorship in mGIST.

Variable	Total (n=111)	15-year nonsurvivors (n=92)	15-year survivors (n=19)	p-value
Synchronous metastases	53 (47.7%)	43 (46.7%)	10 (52.6%)	0.64
Metachronous metastases	58 (52.2%)	49 (53.3%)	9 (47.4%)	0.7
Primary tumor size, cm (median, IQR)	8 (5.5-11.5)	8 (5.5-12)	8.1 (5.7-10.5)	0.79
Underwent metastasectomy	57 (51.4%)	42 (45.7%)	15 (78.9%)	0.008
Underwent metastasectomy before imatinib resistance	39 (35.1%)	27 (29.3%)	12 (63.2%)	0.04
Underwent metastasectomy after imatinib resistance	15 (13.5%)	12 (13.0%)	3 (15.8%)	0.75
Time to metastasectomy, months (median, IQR)	6 (16-42.5)	16 (6-41)	9 (4-86)	0.84
Development of imatinib resistance	69 (62.2%)	60 (65.2%)	9 (47.4%)	0.14
Time to imatinib resistance, months (median, IQR)	42 (22-81)	35.5 (20.5-63.3)	125.5 (95-149.5)	<0.00001

11526 Poster Session

Second-line treatment patterns and outcomes of advanced gastrointestinal stromal tumor: A real-world study.

Xinhua Zhang, Anni Chen, Jun Zhang, Hao Sun, Miao Liu, Xingyu Feng, Xiaojun Wu, Huaiming Wang, Yuan Yin, Xiaoting Wu, Zhi Ding, Yongdong Jin, Minghui Pang, Zhuofei Li, Lie Wang, Ling Fan, Yong Liu, Xu Che, Mengqiao Wang, Yanzhe Xia; Department of Gastrointestinal Surgery, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, Chongqing, China; Gastrointestinal Cancer Center, Chongqing University Cancer Hospital, Chongqing, China; Chongqing University Cancer Center, Chongqing, China; Guangdong Academy Of Medical Sciences & Guangdong General Hospital, Guangzhou, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China; The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; West China Hospital, Chengdu, Sichuan, China; West China Hospital, Sichuan, China; Sichuan Cancer, Sichuan, China; Sichuan Cancer Hospital, Chengdu, China; Sichuan Provincial People's Hospital, Chengdu, China; Peking University Shenzhen Hospital, Shenzhen, China; No. 900 Hospital of the Joint Logistics Support Force, Fuzhou, China; Guangyuan Central Hospital, Sichun, China; People's Hospital of Deyang City, Deyang, China; Department of Hepatobiliary Surgery, Cancer Hospital Chinese Academy of Medical Sciences Shenzhen Center, Shenzhen, China; The Fifth People's Hospital of Chengdu, Chengdu, China; The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Ripretinib has emerged as a promising second-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumors (GISTs), demonstrating comparable efficacy to sunitinib and a superior safety profile. However, the optimal second-line therapy tailored to individual patient characteristics remains underexplored. This prospective, multicenter, observational study (NCT05440357) aims to evaluate real-world patterns and outcomes for GISTs patients. **Methods:** The choice of second-line regimen was determined by the investigators. The primary endpoint was progression-free survival (PFS). Secondary endpoints included safety, objective response rate (ORR), and overall survival (OS). **Results:** From October 2022, 99 patients were enrolled (ripretinib, n = 49; sunitinib, n = 47; regorafenib, n = 3), with a median follow-up of 8.0 months. Among ripretinib-treated patients, 69% (34/49) had primary KIT exon 11 mutations, while 47% (22/47) of sunitinib-treated patients had primary KIT exon 9 mutations. The objective response rates were 20% (10/49) for ripretinib, 9% (4/47) for sunitinib, and 0% for regorafenib. Median PFS (mPFS) for ripretinib, sunitinib and regorafenib was 11.4, 12.4 and 2.8 months, respectively (p = 0.296). Ripretinib demonstrated better mPFS in patients with primary KIT exon 11 mutations compared to sunitinib group (11.4 vs 7.0 months, p = 0.048). In patients with KIT exon 9 mutations, mPFS was 15.0 months for sunitinib. Ripretinib was associated with fewer grade 3/4 treatment-emergent adverse events (TEAEs) compared to sunitinib (10%vs 26%, p = 0.044). OS data are currently immature. Additionally, 27% (13/49) of patients treated with ripretinib and 17% (8/47) with sunitinib underwent surgery. Among patients who underwent surgery following ripretinib treatment, 84.6% (11/13) achieved R0/R1 resection. 100% (8/8) patients achieved R0/R1 resection in sunitinib group. Median postoperative PFS for ripretinib and sunitinib was 15.5 months and 10.2 months, respectively (p = 0.350). **Conclusions:** This study is the first prospective, multicenter, real-world study to compare different second-line targeted drugs for advanced GISTs. Our preliminary results suggest that ripretinib may offer superior clinical benefits for patients with primary KIT exon 11 mutations after failure of imatinib first line treatment. Its favorable safety profile and improved tumor response rate facilitated a higher rate of surgical intervention compared to sunitinib. The benefit of surgery remains to be observed. Clinical trial information: NCT05440357. Research Sponsor: None.

11527 Poster Session

Long-term outcomes in GIST Trial 13-162: Phase II study of imatinib in combination with binimetinib in untreated patients with advanced gastrointestinal stromal tumor (GIST).

Yudi Bao, Mengyuan Liu, Li-Xuan Qin, Ciara Marie Kelly, Lauren Baker Banks, Sandra P. D'Angelo, Mark Andrew Dickson, Mrinal M. Gounder, Mary Louise Keohan, Robert G. Maki, Sujana Movva, Evan Rosenbaum, Vishu Avutu, Brian R. Untch, Aimee Marie Crago, Sinchun Hwang, Samuel Singer, Cristina R. Antonescu, William D. Tap, Ping Chi; Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan-Kettering Cancer Center - Fellowship (GME Office), New York, NY; Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; MSKCC, New York, NY

Background: ETV1 and KIT are lineage-specific master transcriptional and signaling survival factors in GIST. Dual lineage targeting of ETV1 by binimetinib and KIT by imatinib are synergistic in suppressing GIST tumorigenesis and growth in preclinical models. We previously reported positive data in a single-arm phase II study that the combination of binimetinib plus imatinib is highly effective with expected and manageable treatment-associated toxicities, in patients (pts) with treatment-naïve advanced GIST, (ASCO 2020 and https://ascopubs.org/doi/pdfdirect/10.1200/JCO.21.02029). Here, we present 10-year follow-up results. **Methods:** This trial is a single-center, single-arm, phase II study. Adult patients with unresectable or metastatic treatment-naïve GISTs received imatinib (400mg daily) and binimetinib (30mg twice daily), 28-day cycles. The clinical efficacy was evaluated using serial imaging every 8-12 weeks, per RECIST1.1 criteria including objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). Correlatives included tumor genomics, transcriptomes, and imatinib trough levels. **Results:** At data cutoff of Nov 21, 2024, 29/42 evaluable pts with advanced GIST of all genotypes, including 3 *KIT/PDGFRA*-WT, had confirmed RECIST1.1 partial response (PR). Best ORR was 69.0% (95% CI, 52.9% to 82.4%). Median PFS (mPFS) was 36.7 months (95%CI, 24.2 to not estimable [NE]). Median OS (mOS) was 92.5 months (95%CI, 61.0 to NE), and the median DSS (mDSS) was 93.2 months (95%CI, 92.5 to NE). 23/42 pts had undergone surgery, with R0/R1 resection in 18 patients. 7 pts were considered exceptional responders, whose pathology revealed ≥90% significant pathological responses (SPR) and remained no evidence of disease (NED) after surgery ≥45 months. 3 pts who did not have SPR and remained NED ≥58 months. Transcriptome and genomic analysis, and imatinib trough level in the presence of binimetinib are forthcoming. **Conclusions:** The 10-year follow-up analysis of the binimetinib plus imatinib combination phase II study demonstrated robust and sustained clinical benefit in PFS, OS and DSS for patients with treatment-naïve advanced GIST. The combination strategy warrants further evaluation in direct comparison with imatinib in the frontline treatment of GIST. Clinical trial information: NCT01991379. Research Sponsor: Pfizer; FDA R01.

11529 Poster Session

Predicting transposable element-derived neoantigens in ATRX-mutated sarcoma.

Simon Cao, Ziyang Wang, Benjamin Alexander Nacev; UPMC Hillman Cancer Center, Pittsburgh, PA; University of Pittsburgh School of Medicine, Pittsburgh, PA; University of Pittsburgh Department of Medicine, Pittsburgh, PA

Background: Epigenetic dysregulation is a key mechanism in cancer biology, driving both immune evasion and the generation of potentially druggable neoantigen targets. Transposable elements (TEs) are proviral sequences mostly found in epigenetically repressed genomic regions. In cancer, TEs are one potential source of neoantigens. The tumor suppressor gene *ATRX* is an epigenetic regulator that is lost in up to 30% of soft tissue sarcomas. Loss of function of this heterochromatin modulator leads to widespread alterations to transcription patterns. Our prior work in sarcoma, along with studies in other tumors, showed that ATRX loss leads to the de-repression of TEs. We hypothesize that this mechanism leads to TE neoantigen presentation on MHC class I (MHC-I) molecules. **Methods:** Leveraging the gEVE database of proviral sequences with open reading frames, we examined the differential expression of TEs using RNA sequencing of multiple models comparing ATRX lost and ATRX wild-type tumors. Analysis included our previously published data from human undifferentiated pleomorphic sarcoma cell lines (2 clones, 3 replicates per group; GEO: GSE240030) and a publicly available dataset from a mouse model of soft tissue sarcoma (n = 3 per group; GEO: GSE167537). Additionally, we analyzed analogous data from a mouse model of glioblastoma multiforme (GBM), another malignancy with frequent ATRX loss (n = 3 per group; GEO: GSE178113). RNA-seq data was analyzed using Salmon for transcript-to-genome pseudo-alignment, DESeq2 for differential TE expression analysis, and arcasHLA for sample-level MHC-I subtype identification. Differentially overexpressed TEs in ATRX mutant tumors were analyzed for predicted neoantigens using the NetMHCpan4.1 package. **Results:** Across multiple models, ATRX loss of function alterations were associated with both activation and repression of TEs. Within two sarcoma contexts, upregulated TEs were found to have protein-coding sequences with the potential to lead to MHC-I neoantigen presentation. Within a human undifferentiated pleomorphic sarcoma cell line with ATRX loss, there were 7 upregulated TEs shared between the clones, each predicted to contain 12 – 50 MHC-I binding epitopes. Within a mouse soft tissue sarcoma model, 7 TEs were upregulated with ATRX loss, each with 5 – 28 MHC-I binding epitopes. Since ATRX loss alters TE expression in other malignancies, parallel data from a mouse GBM model was additionally analyzed. In this model, 308 TEs were found to be upregulated with ATRX loss, and all were predicted to generate neoantigens. ERVs and LINE1 elements were recurrently identified, making up 97 – 100% of the activated TEs. **Conclusions:** Transposable element transcription altered by ATRX loss in sarcoma and GBM creates a predicted source of MHC-I-binding neoantigens. These neoantigens come from TEs of the ERV and LINE1 families. Research Sponsor: Damon Runyon Cancer Foundation; CI-124-23.

11530 Poster Session

Spatial and bulk transcriptomic analysis of skin Kaposi sarcoma lesions: Differences by disease characteristics.

Quashawn Rakeem Chadwick, Ned Cauley, Nina Bubunenko, Xiaolin Wu, Bahman Asfari, Laura Bassel, Maria Hernandez, Xiaofan Li, Kathryn Lurain, Robert Yarchoan, Joseph Ziegelbauer, Noemi Kedei, Laurie Krug, Ramya Ramaswami; National Institutes of Health, Bethesda, MD; CCR Collaborative Bioinformatics Resource, Center for Cancer Research, NCI, Bethesda, MD; CCR Genomics Technology Laboratory, Frederick National Laboratory, Frederick, MD; Nation Institutes of Health, Bethesda, MD; Center for Advanced Preclinical Research, Frederick National Laboratory, Frederick, MD; Spatial Imaging Technology Resource, Center for Cancer Research, NCI, Bethesda, MD; NCI/NIH, Bethesda, MD; HIV/AIDS Malignancy Branch, CCR, NCI, Bethesda, MD

Background: Kaposi sarcoma (KS) is an angioproliferative tumor caused by Kasposi sarcoma herpesvirus (KSHV) that typically manifests as skin lesions. Other KSHV-associated disease (KAD) that can occur with KS include multicentric Castleman disease (MCD), primary effusion lymphoma (PEL) and KSHV-associated inflammatory cytokine syndrome (KICS). KS with concurrent KAD, which occurs frequently in people with HIV (PWH), contributes to morbidity and mortality. Novel sequencing technologies that evaluate archival KS may further our understanding of HIV-associated KS pathogenesis. **Methods:** Gene expression profiling of archival KS skin samples of 42 PWH was performed with the custom nCounter PanCancer ImmunoOncology panel with the addition of KSHV probes. Spatial RNA profiling was performed using GeoMx digital spatial profiling (DSP) platform on 4 formalin fixed paraffin-embedded tissue sections randomly selected from patients (pts) with concurrent KS and KAD. LANA, CD45, and CD31 expression in samples identified KS ($LANA^+$, $CD31^{+)}$) and other areas of interest (AOIs) including vessels ($LANA^-$, $CD31^+$) and immune cells ($CD45^+$) on tissue sections. Gene Set Enrichment analysis was performed using R package ClusterProfiler. **Results:** Samples were taken from 42 men with HIV with a median age of 40 years. The median CD4 T cell count was 211 cells/ μl and a median HIV viral load of 27 copies/ml. Fifty-two percent of pts with KS had a concurrent KAD, most commonly KICS with KS (30%) followed by MCD with KS (19%). In nCounter analyses, samples from pts with KS alone demonstrated upregulation of STC1, a secreted glycoprotein, (log2FC=2.02, padj=0.001) and MKI67, a proliferation marker, (log2FC=1.11, padj=0.02) as compared to pts with KS and concurrent KAD. Pathway analyses highlighted reduced enrichment in specific cytokine activity profiles (padj = 0.01), natural killer cell activation markers (padj=0.02), and B cell proliferation (padj=0.004), in KS with concurrent KAD specimens. Cell deconvolution analyses showed increased abundance of CD8 T cells and regulatory T cells in KS alone specimens as compared to those with KS and other KAD. DSP of 4 samples of pts with KS and concurrent KAD (2 pts with MCD+ KS, 2 pts with KICS+ KS) identified higher expression of TSPAN (log2FC=1.32, padj=0.04) and LYVE1 (log2FC=1.82, padj=9.17e-5) in LANA+ tumor regions than vessel and immune AOIs, and lower ICAM1 (log2FC=-1.08, padj=3.95e-6), highlighting the role of virus-infected areas in oncogenesis and modulating immune activity. **Conclusions:** Sequencing data of archival HIV-associated KS samples highlighted distinct gene expression profiles by concurrent KAD, particularly in MCD or KICS, demonstrating disruptions in immune activity and increased cell proliferation thus shedding light on the molecular pathways driving KS pathogenesis and avenues for future targeted study.
Research Sponsor: None.

11531 Poster Session

Early assessment of response to chemotherapy via ctDNA in soft tissue sarcoma.

Maggie Yuxi Zhou, Minggui Pan, Nam Bui, Kristen N. Ganjoo; Stanford University School of Medicine, Department of Medicine, Stanford, CA; Stanford Cancer Institute, Palo Alto, CA; Division of Oncology, Department of Medicine, Stanford University, Palo Alto, CA; Stanford Cancer Institute, Stanford, CA

Background: Chemotherapy remains the cornerstone for treatment of soft tissue sarcomas (STS). Biomarkers are needed to enhance timely assessment of chemotherapy efficacy to limit toxicity and guide patient management including estimating prognosis and duration of chemotherapy. **Methods:** This retrospective study includes patients with STS who received chemotherapy in the neoadjuvant or unresectable/metastatic setting at Stanford Sarcoma Center between May 2021 and January 2025. ctDNA was tested with Natera's CLIA lab using a personalized, tumor-informed ctDNA assay (Signatera, bespoke mPCR, NGS assay). Longitudinal changes in peripheral blood ctDNA were correlated with radiographic response and survival. ctDNA response was defined as $>$ 50% decrease in MTM/mL from baseline, with a second confirmatory measurement. Radiographic response was defined as stable disease or partial response on first re-staging assessment after starting therapy. Overall survival (OS) was defined as time from initiation of chemotherapy to death or last clinical follow up. Progression-free survival (PFS) was defined as time from initiation of chemotherapy to radiographic disease progression, death, or last clinical follow up. **Results:** Twenty-six patients (median age at diagnosis = 63 years [range 26 – 78]) were included. Histological subtypes consisted of leiomyosarcoma (uterine [n = 10], extrauterine [n = 4]), malignant peripheral nerve sheath tumor (n = 2), undifferentiated pleomorphic sarcoma (n = 2), angiosarcoma (n = 2), and other (Ewing's sarcoma, malignant phyllodes tumor, perivascular epithelioid cell tumor, low grade myoepithelial carcinoma, high grade uterine sarcoma not otherwise specified, and small round blue cell neoplasm with EWSR1 rearrangement, each n = 1). Chemotherapy consisted of doxorubicin-containing regimens (n = 9), gemcitabine/docetaxel (n = 9), temozolomide-containing regimens (n = 5), and other (cyclophosphamide/topotecan, paclitaxel, and trabectedin, each n = 1). Median follow-up time after initiation of chemotherapy was 12.9 months. 16 of 26 patients had radiographic response. Substantial agreement was observed between ctDNA response and radiographic response (Cohen's kappa coefficient 0.752). Median OS was longer for ctDNA responders (n = 17) than non-responders (n = 9), at 43.8 months vs 20.6 months (p = 0.03). Median PFS was longer for ctDNA responders than non-responders, at 11.4 months vs 2.0 months ($p < 0.001$). In the metastatic cohort (n = 22), time on chemotherapy regimen was longer for ctDNA responders than non-responders, median 5.0 vs 2.6 months, p = 0.016 by Wilcoxon rank sum test. **Conclusions:** Early decline in ctDNA after initiation of chemotherapy correlates with radiographic response and survival in STS. Research is ongoing to evaluate these findings in a prospective study. Research Sponsor: None.

11532 Poster Session

Kaposi sarcoma herpesvirus (KSHV) subtypes and impact on survival in 107 patients with Kaposi sarcoma and other KSHV-associated diseases.

Jose Mercado-Matos, Vickie A. Marshall, Elena M. Cornejo Castro, Wendell Miley, Nazzarena Labo, Romin Roshan, Matthew Witterholt, Robert Yarchoan, Kathryn Lurain, Ramya Ramaswami, Denise Whitby; National Cancer Institute, National Institutes of Health, Bethesda, MD; Leidos Biomedical Research, Inc., Frederick, MD; National Institutes of Health, Frederick, MD; NCI/FNLCR, Frederick, MD; NIH-National Cancer Institute, Frederick, MD; National Cancer Center - NIH, Bethesda, MD; HIV/AIDS Malignancy Branch, CCR, NCI, Bethesda, MD

Background: Kaposi sarcoma herpesvirus (KSHV, also known as human herpesvirus 8) is an oncogenic virus that causes Kaposi sarcoma (KS), one of the most prevalent cancers in people with HIV (PWH) worldwide. KSHV also causes primary effusion lymphoma (PEL), a non-Hodgkin lymphoma, a plasmablastic variant of multicentric Castleman disease (MCD), and KSHV-associated inflammatory cytokine syndrome (KICS). KSHV-associated diseases (KADs) can occur alone or concurrently. The major KSHV genetic subtypes A, A5, B, C, D, E and F, based on the K1 open reading frame (ORF), are distributed by global region of origin. A and C genotypes are seen in Europe and North America whereas B and A5 variants are observed in Africa; D, E and F genotypes were described in isolated populations. There are limited data on the association between KSHV subtypes and survival outcomes. **Methods:** We investigated the ORF K1 subtype, disease characteristics, and impact on survival outcomes in 107 patients (pts) with KADs treated at the HIV/AIDS Malignancy Branch in the United States from 2010-2024. KSHV-DNA was extracted from peripheral blood mononuclear cells (PBMCs), KSHV-positive tissues and body fluids, including effusions. Extracted DNA was tested for KSHV using a CLIA-certified qPCR assay. Samples identified as KSHV-positive by qPCR were sequenced using either next-generation sequencing (NGS) or Sanger sequencing. **Results:** The cohort consisted of predominantly men (94%) and 55% were Black. Ninety-seven percent of pts had HIV (median CD4 count of 216 cells/mm3 and median HIV viral load 189,590 copies/mL). The most common KAD was KS (92%) followed by PEL (36%), MCD (23%), and KICS (22%). However, 64% had more than one concurrent KAD – 20% had KS and PEL. At the time of analysis, 39 (36%) pts were deceased, 26 (24%) had a PEL diagnosis. Seventy-nine percent of pts were from North America, 11% from Latin America and 9% were from sub-Saharan Africa; KSHV genotypes were consistent with a patient's geographic origin. Overall, the most common genotype was A (44%), 30% of pts with genotype A had KS alone and 30% had PEL+/-KS (Table). KSHV subtypes based on K1 did not impact survival outcomes (Global Log-rank P=0.9) overall. In 98 pts with KS with and without other KAD, KSHV subtypes did not affect survival but the presence of concurrent PEL as compared to MCD or KICS lead to worse survival in pts [Hazard Ratio: 7.9 (95% confidence interval: 3.4-18.2, P<0.0001)]. **Conclusions:** In this large cohort of pts with KS and other KAD, KSHV genotype was not associated with survival outcomes. Among pts with KS, concurrent KAD, such as PEL, led to poorer survival. This suggests that clinical manifestations rather than underlying viral variants impacted survival. Research Sponsor: None.

KSHV genotype prevalence (%) by KAD.

Overall %	A 44%	A5 8%	B 11%	C 26%	Dual infection 8%
KS	30	50	17	29	0
MCD +/- KS	11	0	17	14	22
PEL +/- KS	30	25	42	21	22
KICS + KS	17	25	17	29	33
MCD+PEL+/- KS	13	0	8	7	22

11533 Poster Session

Phase ib/II study of fluzoparib in combination with dalpiciclib in patients with locally advanced or metastatic sarcoma.

Anqi Wang, Jinchang Lu, Tianqi Luo, Jin Wang; Musculoskeletal Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Poly ADP-ribose polymerase (PARP) plays a role in DNA damage repair, and PARP inhibitors can exert anti-tumor efficiency in tumors with homologous recombination repair defection (HRD). Cyclin-dependent kinase (CDK) plays an important role in cell cycle regulation. Rb is the direct substrate of CDK4/6, and Rb/E2F participates the HR-mediated DNA repair. Therefore, selective CDK4/6 inhibition can theoretically aggravate HRD and hinder DNA repair of tumor cells treated with PARP inhibitors. Combined of CDK4/6 and PARP inhibitors may provide a potential new drug strategy for sarcomas. **Methods:** FOUNDS is a 2-part, open-label, phase 1/2 study. Key inclusion criteria are: (1) 12-75 years old; (2) Locally advanced or metastatic sarcomas after first-line treatment, with at least one measurable lesion according to RECIST 1.1 criteria. Patients(pts) will receive fluzoparib (0.1 or 0.15 g po., qd, q4w) and dalpiciclib (0.1, 0.125 or 0.15 g po., qd, d1-21, q4w) continuously until progressive disease (PD) or intolerable toxicity occurred. Part 1 is intended to establish the recommended phase 2 dose (RP2D) using a i3+3 dose escalation design. Part 2 will examine the safety and efficacy of fluzoparib + dalpiciclib using the Simon minimax 2 stage design. The primary endpoint is the objective response rate (ORR). **Results:** In the escalation part, 12 pts (median age 22 years) were included. At the data cut-off (Jun. 10, 2025), the median follow-up time was 7.93 month (95% CI 7.03-8.83). The DCR per RECIST v1.1 is 12.5% including 2 pts who achieved a stable disease. The most common treatment-emergent AEs (TEAEs, ≥20%) were leukopenia, neutropenia, etc. 3 pts (25%) had grade ≥3 TRAEs and no drug-related AEs led to death. In Cohort 4, 1 pt experienced dose-limiting toxicity (DLT) of grade 3 thrombocytopenia, and the other 1 pt experienced DLT of severe stun. The RP2D was determined as Fluzoparib 0.1g bid. plus Dalpiciclib 0.15g qd, d1-d21, q4w. **Conclusions:** This novel combination therapy of CDK4/6 inhibitor and PARP inhibitor showed manageable toxicity that could provide a strategy for advanced or metastatic sarcoma. Part 2 to evaluate safety and efficacy is currently recruiting pts. Clinical trial information: NCT05952128. Research Sponsor: Jiangsu Hengrui Pharmaceutical Co., Ltd.

TRAEs with an incidence of ≥30% and any grade ≥3 TRAEs.

Cohort	1	2	3	4	Total
Dose every 4 weeks (q4w)	0.1g	0.1g	0.1g	0.15g	
Fluzoparib bid. + Dalpiciclib qd. d1-d21	+0.1g	+0.125g	+0.15g	+0.15g	
N	4	3	3	2	12
TEAEs, n (%)					
All grades	4(100)	3(100)	3(100)	2(100)	12(100)
Leukopenia	3(75)	3(100)	3(100)	1(50)	10(83)
Neutropenia	3(75)	2(67)	3(100)	1(50)	9(75)
Anemia	1(25)	1(33)	3(100)	2(100)	7(58)
Vomiting	2(50)	2(67)	1(33)	1(50)	6(50)
Thrombocytopenia	2(50)	2(67)	1(33)	1(50)	6(50)
Diarrhea	1(25)	1(33)	1(33)	1(50)	4(33)
Cough	1(25)	1(33)	2(67)	0(0)	4(33)
Fever	2(50)	1(33)	0(0)	0(0)	3(25)
Stun	0(0)	1(33)	1(33)	1(50)	3(25)
Grade ≥3	0(0)	1(33)	0(0)	1(50)	2(17)

11534 Poster Session

Advancing precision oncology in soft tissue sarcomas: The role of iTRAC in metastatic risk stratification and treatment personalization.

Fred Chibon, Ataaillah Benhaddou, Gaëlle Pérot, Philippe Rochaix, Thibaud Valentin, Gwenael Ferron; INSERM U1037, Toulouse, France; Magic Genomix, Toulouse, France; IUCT Oncopole, Toulouse, France; Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France

Background: Soft Tissue Sarcomas (STS), known for their extensive Genomic instability (GIN), often result in poor clinical outcomes. Grading systems, such as FNCLCC, have limited prognostic accuracy in stratifying metastatic risk for STS patients. We introduce transcription-associated GIN indice (iTRAC) to improve prognostic precision and guide treatment decisions. **Methods:** This study analyzed 226 STS tumor samples using RNA sequencing (RNAseq) to assess breakpoint distribution from fusion transcripts as a surrogate for GIN. We calculated iTRAC to quantify transcription-associated GIN. Kaplan-Meier survival analysis were used to evaluate prognostic relevance in patients receiving or not chemotherapy. Multivariate analysis was performed to evaluate the iTRAC compared to FNCLCC and CINSARC for metastatic risk stratification. **Results:** STS patients with medium iTRAC level had the poorest metastasis-free survival (MFS) compared to low and high iTRAC levels. Importantly, patients with low iTRAC have a poorer outcome when treated with chemotherapy than those untreated, but at the contrary patients with medium iTRAC and treated by chemotherapy have a better outcome, raising the question of the potential predictive value of iTRAC for adjuvant chemotherapy in STS patients. FNCLCC and CINSARC groups did not show significant difference in MFS between treated and not treated patients. **Conclusions:** iTRAC is a novel biomarker for stratifying metastatic risk and guiding personalized treatment in STS. It outperforms molecular and histological prognosis systems like CINSARC and FNCLCC grade by revealing distinct MFS between patients receiving or not chemotherapy. This could enable better identification of patients who may benefit from chemotherapy and alternative options for those with poor responses. Prospective clinical trials are needed for validation and integration for patients care.
Research Sponsor: None.

11536 Poster Session

Molecular subtyping and insights into sarcoma biology and prognosis.

Aleksei Shevkoplias, Angelina Khachatryan, Vladimir Kushnarev, Konstantin Chernyshov, Nikita Kotlov, Oleg Baranov, Nathan Hale Fowler; BostonGene Corporation, Waltham, MA

Background: Sarcomas represent a diverse group of mesenchymal malignancies, with over 200 subtypes recognized by the WHO. This heterogeneity, combined with rarity, complicates diagnosis. Here, comprehensive molecular profiling and unsupervised clustering were applied to define sarcoma subtypes associated with differentiation, genomic events, and prognosis. **Methods:** Whole exome and transcriptome sequencing was performed on 1,046 sarcoma samples via the BostonGene Tumor Portrait test. Hierarchical expression-based clustering was integrated with somatic mutations, fusions, copy number alterations, genome segmentation, and signatures, validated on 23 external datasets (n = 1,678). **Results:** Nine molecular clusters (C1-C9) reflecting distinct biological patterns were identified (Table). Stable, lineage-restricted clusters included leiomyosarcoma (C2) marked by smooth muscle differentiation pathways and *TP53*, *ATRX*, and *RB1* mutations; vascular sarcoma (C7) with vascular signaling and angiogenic amplifications; synovial sarcoma (C6) defined by *WNT* activation and *SS18-SSX* fusions; and Ewing sarcoma (C9) characterized by neuronal development signatures and *EWSR1-FLI1* fusions. Clusters progressing toward undifferentiated pleomorphic sarcoma (UPS)-like phenotypes included liposarcoma (C3) progressing from adipocyte differentiation with *MDM2/CDK4* amplifications; chondrosarcoma/chordoma (C5) transitioning from cartilage development pathways with TGFβ activation; and bone and UPS-like (C1) characterized by angiogenesis signatures, genomic instability, *TP53* mutations, and the poorest survival (log-rank $p < 0.05$). Molecular clusters predicted survival regardless of the specific diagnosis. For example, liposarcoma and leiomyosarcoma patients in cluster C1 had a worse prognosis than those in C2 with the same diagnosis. **Conclusions:** The proposed molecular subtypes simplify sarcoma classification, providing unique prognostic insights missing in the current diagnostic framework. These findings suggest molecular subtypes could offer valuable knowledge for sarcoma research and patient treatment. Research Sponsor: None.

Characterization of molecular sarcoma subtypes.

Cluster	Predominant diagnoses	Undifferentiation progression	Biology	Alterations (chi-sq p < 0.01)
C1	Bone and UPS-like	Progressing	Undifferentiated or nearly undifferentiated	*TP53* mutation (35%)
C2	Leiomyosarcoma	Stable	Smooth muscle differentiation	*TP53* (53%), *ATRX* (18%), *RB1* (15%) mutations
C3	Liposarcoma	Progressing	Adipocyte differentiation	*MDM2/CDK4* amplifications (45%)
C4		Progressing	Biologically diverse	
C5	Chondrosarcoma, chordoma	Progressing	Cartilage development	
C6	Synovial sarcoma	Stable	WNT activation	*SS18-SSX* fusions (68%)
C7	Vascular sarcoma	Stable	Vascular signalling, angiogenesis	
C8		Progressing	Biologically diverse	
C9	Ewing sarcoma	Stable	Neuronal development signatures	*EWSR1-FLI1* fusions (92%)

11537 Poster Session

Early on-treatment ctDNA dynamics and response by imaging in patients with sarcoma.

Adrienne I. Victor; University of Rochester, Rochester, NY

Background: ctDNA holds promise as a prognostic and predictive biomarker for risk stratification and treatment response monitoring across multiple tumor types. However, the optimal timepoints and cutoffs for interpretation of ctDNA results are not well defined. Here we explored the ctDNA dynamics in patients with sarcomas on cytotoxic chemotherapy, with a focus on early time points to predict response. **Methods:** All sarcoma patients at the Wilmot Cancer Institute who had ctDNA (SignateraTM, Natera, Inc.) requested clinically from 03/01/22 – 12/31/25 were screened. Patients who had a positive baseline and at least 2 cycles of cytotoxic chemotherapy with serial ctDNA monitoring and response evaluation were selected for further analysis. Response was determined by imaging reports (CT, MRI, or PET) after 2-4 cycles of therapy. **Results:** One hundred and twenty-four patients were identified on initial screening, and 112 were able to generate a bespoke assay. Twenty-two patients met criteria for early on-treatment response analysis and 4 had results available from a second line of chemotherapy, for a total of 26 evaluations. Seventeen patients had metastatic disease while 5 were on neoadjuvant chemotherapy for high risk localized sarcomas. The most common sarcoma subtype was LMS (5), followed by undifferentiated small round cell sarcoma (Ewing, other EWSR1 fusions, BCOR; 4 patients), and osteosarcoma (3). Most patients, including those who progressed, showed some early decrease in ctDNA levels, but no patients whose ctDNA result converted to negative within the first two cycles progressed on the first reassessment. In this series a log10 fold change of -1.25 or greater by the end of cycle 2 separated responders and progressors. **Conclusions:** ctDNA is promising as an early biomarker of response across a wide variety of sarcoma subtypes and chemotherapy regimens. ctDNA dynamics may provide particular clinical utility in interpreting scans showing stable disease, as well as when response is difficult to capture on imaging, such as bony primaries or metastasis, or infiltrative malignancies such as angiosarcoma. Larger data sets and multi-institutional collaboration are needed to verify optimal time points and cutoffs for guiding patient care and interventional trials. Research Sponsor: None.

Log10 change in ctDNA from baseline at end of cycle 1 and cycle 2 chemotherapy by initial imaging response.

Initial Response	Cycle 1 median log change	Cycle 1 log change range	Cycle 2 median log change	Cycle 2 log change range
Progression	-0.17	-1.01— +0.16	-0.36	-1.23— +0.21
Stable disease (SD)	-0.18	ND (Not Detected) — +0.27	-0.88	ND — +1.00
Partial response (PR)	-1.62	ND — -0.21	-2.42	ND — -1.26
Complete response (CR)	-2.72	ND — -1.00	-3.12	ND — -2.35
PR + CR	-2.35	ND — -2.01	-2.08	ND — +1.00
SD + PR + CR	-1.80	ND — +0.27	-2.47	ND — -1.26

11538 Poster Session

MicroRNA-based biomarkers of outcome in soft tissue sarcoma treated with hypofractionated preoperative radiation therapy.

Joanne B. Weidhaas, Kristen McGreevy, John Nikitas, Anusha Kalbasi, Vishruth Reddy, Donatello Telesca; University of California, Los Angeles, Los Angeles, CA; MiraDx, Los Angeles, CA; University of California, Department of Radiation Oncology, Los Angeles, CA; Stanford University, Stanford, CA; UCLA, Department of Radiation Oncology, Los Angeles, CA; Department of Biostatistics, University of California, Los Angeles, Los Angeles, CA

Background: Soft tissue sarcomas (STS) are rare, aggressive malignancies with high variability in response to radiation therapy (RT). Our previous research in a small cohort who received preoperative hypofractionated RT (SBRT) on a phase II trial suggested that germline microRNA-based single nucleotide polymorphisms (mirSNPs) could identify patients at increased risk of major wound toxicity (MWT). This study explores the potential of this class of biomarker to predict MWT and additional outcomes to preoperative SBRT in STS. These findings could guide personalized treatment strategies and possibly the choice of RT regimen in the future. **Methods:** We analyzed 110 patients with high-risk extremity or trunk STS treated with five-day preoperative SBRT (30 Gy in five fractions). Over 100 mirSNPs were evaluated for their ability to predict RT outcomes, including late toxicity, MWT, distant metastases, and pathological response. Pathological response was defined as a necrosis score >= 70, late toxicity as grade >=2 at 2 years, and MWT as grade >= 3. Preliminary genetic models were developed using elastic net, random forest, and boosted tree algorithms and evaluated using leave-one-out cross-validation (LOOCV) performance metrics. mirSNPs were pre-filtered using Fisher or Jonckheere-Terpstra p-values (<0.2) for relevance to outcomes. **Results:** We developed preliminary genetic signatures to accurately predict 4 different outcomes in sarcoma patients undergoing preoperative SBRT: late toxicity (AUC=0.830), distant failure (AUC=0.775), pathological response (AUC=0.765), and major wound toxicity (AUC=0.736). Our pathological response genetic model has balanced sensitivity (0.750) and specificity (0.781), suggesting it could reliably predict which patients respond well to SBRT. **Conclusions:** Our study highlights the promise of mirSNP-based models in predicting STS outcomes to preoperative SBRT. By identifying patients with favorable versus unfavorable responses, these models could help identify patients who could be considered for preoperative SBRT versus standard fractionated radiation, as there may be fractionation-dependent radiation toxicity in sarcoma, as has been identified in other malignancies. Future directions include investigating associations among identified outcomes, inclusion of additional clinical variables, and comparison to toxicity with preoperative standard fractionated radiation. These efforts are significant steps towards paving the way for more personalized sarcoma care. Clinical trial information: NCT02701153. Research Sponsor: None.

LOOCV performance metrics in sarcoma data (n=110).

Outcome	Sensitivity	Specificity	PPV	NPV	F1 Score	AUC
Any Late Toxicity (Grade 2 at 2 Years)	0.786	0.875	0.478	0.966	0.595	0.830
Distant Failure	0.680	0.871	0.607	0.902	0.642	0.775
Path Response (Necrosis Score >= 70)	0.750	0.781	0.600	0.877	0.667	0.765
Major Wound Toxicity	0.667	0.805	0.595	0.849	0.629	0.736

11539 Poster Session

Circulating free DNA derived from active chromatin as a predictive biomarker for clinical benefit to checkpoint inhibitor-based therapies in metastatic leiomyosarcoma.

Carlos Diego Holanda Lopes, Hsin-Ta Wu, Abdulazeez Salawu, Lee-Anne Stayner, Katharine Dilger, Abha A. Gupta, Aaron Richard Hansen, Anna Spreafico, Philippe Bedard, Maggie C Louie, Lillian L. Siu, Albiruni Ryan Abdul Razak; Princess Margaret Cancer Centre – University Health Network, University of Toronto, Toronto, ON, Canada; Aqtual, Hayward, CA; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Aqtual, Inc., Hayward, CA; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Princess Margaret Cancer Consortium, Marathon of Hope Cancer Centres Network, Toronto, ON, Canada

Background: Leiomyosarcoma (LMS) is a common subtype of soft tissue sarcoma with a poor prognosis in the metastatic setting. LMS shows minimal benefit from monotherapy immune checkpoint inhibitors (CPI), however combinatorial CPI strategies may be effective in part due to tumor enrichment of epigenetic alterations. The DAPPER trial (NCT03851614) was a randomized, single center phase II study of durvalumab combined with olaparib or cediranib. Of the 30 LMS patients enrolled, 36.3% (n = 11) experienced disease stabilization or shrinkage. The present study aims to leverage a novel active chromatin cell-free DNA ($cfDNA_{ac}$) platform to investigate the epigenetic and genomic profiles of LMS patients in the DAPPER trial, with the goal of identifying biomarkers associated with clinical benefit from CPI-based therapies. **Methods:** Baseline plasma samples (n = 30) from LMS patients in the DAPPER trial were processed using a proprietary $cfDNA_{ac}$ capture assay that enriches active chromatin cfDNA. Following whole genome sequencing, univariate analysis and machine learning-based recursive feature selection were used to identify genomic features associated with clinical benefit rate (CBR, defined as RECIST v1.1 complete or partial response, or stable disease lasting $>$ 6 months). **Results:** We identified 918 promoter and exon features that were significantly different ($p < 0.01$) at baseline and could segregate patients who achieved CBR from those who did not. Over-representation analysis of these gene features using Gene Ontology ($p_{adj} < 0.05$) showed enrichment in biological pathways associated with double-strand break repair, inflammatory response, and immune response - specifically T-cell receptor activation and signaling, and macrophage homeostasis in patients with CBR. **Conclusions:** This study highlights the utility of $cfDNA_{ac}$ profiling as a non-invasive method for identifying biomarkers that predict clinical benefit from CPI-based therapy in patients with advanced LMS. Further analyses are ongoing to evaluate whether the genomic-derived features correlate with other clinical outcomes, such as progression-free survival, overall survival, and orthogonal data (e.g. tumor tissue RNA-seq). Research Sponsor: None.

11540 Poster Session

Predictive gene signature for the efficacy of pazopanib in solitary fibrous tumor: A Spanish Group for Research in Sarcoma (GEIS) study.

David Silva Moura, Jesus Lopez-Marti, Silvia Stacchiotti, Ana Sebio, Andres Redondo, Nicolas Penel, Jean-Yves Blay, Xavier Garcia del Muro, Giovanni Grignani, Josefina Cruz Jurado, Javier Martínez-Trufero, Antoine Italiano, Emanuela Palmerini, Daniel Bernabeu, Jose Lucinio Mondaza-Hernandez, Nadia Hindi, Javier Martin Broto; Health Research Institute-Fundación Jiménez Díaz University Hospital, Autonomous University of Madrid (IIS-FJD, UAM), Madrid, Spain; Research Health Institute of Fundcacion Jimenez Diaz, Madrid, Spain; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Hospital Universitario La Paz, Madrid, Spain; Centre Oscar Lambret, Lille, France; Centre Léon Bérard, Lyon, France; Medical Oncology Department, Institut Català d'Oncologia IDIBELL Research Institute, University of Barcelona, Barcelona, Spain; Azienda Ospedaliera Città della Salute e della Scienza, Turin, Italy; Hospital Universitario de Canarias; GEICAM Spanish Breast Cancer Group, Tenerife, Spain; Instituto Aragonés de Investigación Sanitaria, Hospital Universitario Miguel Servet, Zaragoza, Spain; Early Phase Trials Unit, Institut Bergonié, Bordeaux, France; Osteoncologia, Sarcomi dell'Osso e dei Tessuti Molli, e Terapie Innovative - IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy; Fundación Jimenez Diaz University Hospital, Madrid, Spain; University Hospital General de Villalba, Madrid, Spain; Instituto de Investigacion Sanitaria Fundacion Jimenez Diaz (IIS/FJD; UAM), Madrid, Spain; Fundación Jimenez Diaz University Hospital, Madrid, Spain

Background: Pazopanib was shown to be active in advanced Solitary Fibrous Tumor (SFT), with 58% and 51% of the typical and malignant/ dedifferentiated SFT patients, achieving an objective response by Choi criteria, in an international phase II clinical trial led by our team. Nonetheless, predictive biomarkers of pazopanib efficacy represent a clinical unmet need, to support the rational selection of this drug in this histology. We presented here a predictive transcriptomic-based signature for the efficacy of pazopanib in SFT. **Methods:** Patients enrolled in the GEIS 32 trial (ClinicalTrials.go ID: NCT02066285), testing pazopanib in two separate cohorts of SFT (typical and malignant/ dedifferentiated SFT), and with available tumor samples, were included in this study. Gene expression was assessed by direct transcriptomics, using the HTG EdgeSeq Oncology Biomarkers Panel (HTG Molecular Diagnostics, Inc.; Tucson, AZ, USA), according to manufacturers' instructions. Raw counts were normalized by variance stabilizing transformation (VST) using DESeq2. Univariate Cox regression analysis was performed to identify the genes significantly associated with progression-free survival (PFS; $p < 0.01$). These remaining genes were used as input to build a gene expression signature, using a multivariate Cox regression applying a Lasso penalty (10-fold cross-validation). Risk scores were calculated by multiplying the expression of every gene with its corresponding Cox regression coefficient. **Results:** A series of 40 patients was included for data analyses, with a median age of 64 years old, 62.5% being females, and a median follow-up from pazopanib treatment of 18 months. A total of 24 (60%), 14 (25%), and 2 (5%) patients were diagnosed with malignant, typical, or dedifferentiated SFT, respectively. The predictive signature of pazopanib efficacy was built with 18 genes, identified as significant in the univariate analysis, applying the Lasso penalty. This signature included 13 and 5 genes associated with resistance or sensitivity to pazopanib, respectively. Genes overexpressed and associated with low PFS of pazopanib included *CKS2*, *FANCA,* KPNA2, and *CXL14*, among others. Patients in the high-risk gene signature group (N = 23) showed a significantly worse PFS for pazopanib treatment, compared with patients in the low-risk group (N = 17): [5.6 months (95% CI 3.7-10.0) vs. 10.0 months (95% CI 6.5-NR), $p <= 0.012$; HR = 1.25 (95% CI 1.1-1.4, $p < 0.001$]. The cut-off calculated by MAXSTAT was 42.515. **Conclusions:** Our study identified a novel 18-gene-based signature that significantly predicts the efficacy of pazopanib in SFT patients. Future studies will focus on the prospective validation of this predictive gene signature. Research Sponsor: None.

11541 Poster Session

RNA-based fusion NGS panel testing for the improved classification of soft tissue sarcomas: A retrospective analysis.

Suruchi Aggarwal, Sameer Rastogi, Harsha Gowda, Pooja Shri, Charu Bahl, Aparna Natarajan, Jammula Sri Ganesh, Sabba Farhin, Karunakaran Coral, Syed Muqlisur Rehman; MedGenome Labs, Bangalore, India; All India Institute of Medical Sciences (AIIMS), Delhi, India; MedGenome, Inc, Foster City, CA; Medgenome Labs, Bengaluru, India; MedGenome Labs Ltd, Bangalore, India

Background: Accurate diagnosis of soft tissue sarcomas (STS) is critical for effective clinical management. The integration of genetic data enables precise tumor categorization, enhancing diagnostic accuracy. **Methods:** This study presents retrospective molecular classification data of 295 soft tissue sarcoma patients tested using a 110-gene Soft Tissue Sarcoma NGS panel developed at MedGenome Labs, Bangalore, India. The panel facilitates the simultaneous analysis of single nucleotide variants (SNVs), copy number variations, and RNA fusions in a single run. **Results:** Among the 295 cases, clinically relevant fusion or mutation was identified in 186 patients which led to the clarification or reassignment of diagnosis 45/186 (24%) of patients. Key reclassifications included 7 *BCOR*-rearranged sarcomas misdiagnosed as other sarcoma types histologically, 5 *EWSR1::FLI1* cases accurately identified as Ewing's sarcoma, and a myxoid liposarcoma case reclassified as Ewing-like sarcoma based on *EWSR1::TFCP2* fusion. Additional findings included two *HEY1::NCOA2* fusion cases reclassified as mesenchymal chondrosarcoma and a *TAF15::NR4A3* fusion case revised to extraskeletal myxoid chondrosarcoma from synovial sarcoma. Likewise, few other diagnosis revisions are highlighted in the table below. **Conclusions:** These results emphasize the diagnostic utility of broad-panel NGS testing with RNA-based fusion detection, underscoring its significant impact on the accurate classification and improved clinical management of STS patients. Research Sponsor: None.

Few STS types reclassified based on molecular findings.

Histologic Subtype (number of cases)	Molecular classification	Molecular event
Spindle Cell Sarcoma (1)	Dermatofibrosarcoma protuberans	*COL1A1::PDGFB*
Synovial Sarcoma (1)	Endometrial Stromal sarcoma	*ZC3H7B::BCOR*
Spindle Cell Sarcoma (1)	Inflammatory Myofibroblastic Tumor	*CLTC::ALK*
Sarcomatoid carcinoma (1)	Low grade fibromyxoid sarcoma	*FUS::TFCP2*
Angiosarcoma (1); Sarcomatoid Carcinoma (1); Undifferentiated Sarcoma (1)	Mucoepidermoid Carcinoma; Mucoepidermoid Carcinoma; Mucoepidermoid Carcinoma	*NUDT4::MAML2; NR1D1::MAML2; NR1D1::MAML2*
Spindle Cell Sarcoma (1)	Nodular Fascitis	*CALD1::USP6*
Low grade fibromyxoid sarcoma? Synovial sarcoma? (1); Osteosarcoma (1); Rhabdomyosarcoma (1)	Sclerosing Epithelioid Fibrosarcoma; Sclerosing Epithelioid Fibrosarcoma	*FUS::CREB3L1; EWSR1::CREB3L3; FUS::TFCP2*
High grade sarcoma with hemangiopericytomatous pattern (1); Spindle Cell Sarcoma (1)	Synovial Sarcoma; Synovial Sarcoma	*SS18::SSX1; SS18::SSX1*
Epithelioid sarcoma (1); Inflammatory Myofibroblastic Tumor (1)	Uncommon EWSR1 rearranged sarcoma; Uncommon EWSR1 rearranged sarcoma	*EWSR1::ZBTB44; ZC3H7B::EWSR1*
Fibrosarcoma (1)	Undifferentiated Mesenchymal tumours	*YAP1::KMT2A*

11542 Poster Session

Comprehensive molecular analysis of phase II trial of nivolumab in patients with recurrent or metastatic carcinosarcomas.

Kum-Hee Yun, Miso Kim, Su-Jin Shin, Jung Yong Hong, Min Hwan Kim, Young Han Lee, Jeeyun Lee, Sung Hyun Kim, Hyo Song Kim; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; Department of Pathology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; Department of Radiology, Yonsei University College of Medicine, Seoul, South Korea; Samsung Medical Center, Seoul, South Korea; Yonsei University College of Medicine, Seoul, South Korea

Background: We conducted a single-center, prospective, phase II trial to evaluate the efficacy and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, in patients with recurrent or metastatic carcinosarcoma who progressed after prior chemotherapy. Carcinosarcoma, a malignant neoplasm composed of both epithelial and mesenchymal elements, is a rare and aggressive tumor categorized as high-grade cancer by NCCN guidelines. Given the potential for nivolumab to selectively target PD-L1 overexpressing tumor cells, this study aims to identify patients who would likely benefit and orphan malignancy components. **Methods:** In this single arm phase 2 trial (NCT05224999), eligible patients had histologically confirmed metastatic and/or recurrent carcinosarcoma, measurable disease, 1-3 prior chemotherapy, and adequate renal/hepatic/hematologic function. Treatment consisted of nivolumab 3 mg/kg every 2 weeks. We compared the genomic and transcriptomic properties in our carcinosarcoma tissue with those in TCGA sarcoma, TCGA carcinoma, and TCGA uterine carcinosarcoma. **Results:** Between July 2020 and Nov 2023, 28 patients enrolled and received trial treatment. Of the 28 patients evaluable, 4 (14.3%) achieved confirmed partial response, and 11 (39.3%) had stable disease, yielding and disease control rate of 53.6%. The median PFS was 2.6 months. The pre-specified primary endpoint was met with 6-months PFR of 30.8%. NGS analysis revealed that carcinosarcoma shares molecular features with both carcinoma and sarcoma, while also exhibiting unique genetic and transcriptional profiles. While some molecular characteristics were common across all three tumor types, carcinosarcoma also displayed unique genetic alterations and transcriptional patterns, underscoring its distinct molecular identity. When comparing our genomic data to TCGA datasets, we observed overlapping mutations. In carcinosarcoma, frequently altered genes included TP53 (sarcoma), ZFHX3 (carcinoma), CHD4 (sarcoma), IRS1 (sarcoma), ARID1A (both), ABL1 (sarcoma), MED12, and PIK3CA (carcinoma). These findings suggest potential shared molecular mechanisms and emphasize the unique genomic landscape of carcinosarcoma. **Conclusions:** Carcinosarcoma comprises features shared with carcinoma and sarcoma, along with distinct characteristics unique to this tumour type. These findings highlight the distinct molecular landscape of carcinosarcoma and pave the way for more precise, biomarker-driven therapeutic approaches. Furthermore, patients were stratified based on the degree of molecular similarity to carcinoma or sarcoma, enabling exploratory analyses to assess the potential relationship between these stratifications and drug response. Clinical trial information: NCT05224999. Research Sponsor: None.

11543 Poster Session

Neutrophil-to-lymphocyte ratio as a clinical biomarker for immune checkpoint inhibitor response in advanced sarcoma.

Gabriel Tinoco, Marium Husain, David A. Liebner, James Lin Chen, Erin A. Fetzer, Alyson McMahon, Xiaokui Mo, Athanasios Papadas, Pradyoth Sirineni, Kyle Hansotia; Division of Medical Oncology, The Ohio State University, Arthur G. James Comprehensive Cancer Center, Columbus, OH; The Ohio State University Medical Center, Columbus, OH; The Ohio State University Wexner Medical Center, Columbus, OH; The James, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Ohio State University, Columbus, OH; The Ohio State University, Center for Biostatistics, Columbus, OH; The Ohio State University, Columbus, OH

Background: As immunotherapy gains traction in sarcoma treatment, identifying biomarkers and understanding patterns of response to immune checkpoint inhibitors (ICI) remain critical. We expanded a prior cohort to investigate clinical factors, including the neutrophil-to-lymphocyte ratio (NLR) and its changes, in predicting outcomes such as overall survival (OS) and progression-free survival (PFS) in advanced sarcoma. **Methods:** Patients from The Ohio State University Sarcoma Clinics (2015–2023) were included in a retrospective ICI database. Data included treatment regimens (single-agent ICI or ICI+combination therapy) and clinical variables, particularly baseline and post-treatment NLR stratified into low (< 5) or high (≥ 5). Survival outcomes were analyzed using log-rank tests and Cox regression to assess OS and PFS. **Results:** A total of 192 patients met the inclusion criteria. Most were male (55%), and 83% had Stage 4 disease at ICI initiation. ICI was started as a third-line or later therapy in 52% of cases. The majority received single-agent ICI (57%), while 43% underwent ICI+combination therapy with other modalities (e.g., surgery, radiation, TKI). OS and PFS were similar between single-agent ICI and ICI+combination groups (OS: $p = 0.419$; PFS: $p = 0.834$), though clinical variables in the ICI+combination group may confound results. Median OS was 60 weeks, and median PFS was 40 weeks. Significant differences in OS and PFS were associated with NLR. Patients with lower NLR had improved OS ($p < 0.0001$). Among those with higher NLR at ICI initiation, OS improved with ICI+combination therapy ($p = 0.039$). After the first ICI cycle, the OS benefit persisted for patients with high NLR ($p < 0.0001$), regardless of treatment type. However, survival did not differ by treatment modality or by changes in NLR from baseline ($p = 0.710$). For PFS, patients with low NLR at ICI initiation had improved outcomes ($p = 0.0002$). Further analysis showed no PFS differences by NLR in the ICI+combination group. After the first cycle, the PFS benefit for low NLR persisted ($p = 0.0006$). Conversely, an increased NLR ratio from baseline to the first cycle was linked to worse PFS ($p = 0.003$), particularly in the ICI+combination group ($p = 0.0029$) but not in single-agent ICI ($p = 0.8630$). OS and PFS were not influenced by age, gender, or histology. **Conclusions:** NLR is a promising clinical biomarker for predicting response to ICI in advanced sarcoma. Low baseline NLR predicts improved OS and PFS, while changes in NLR may indicate progression risk. These findings warrant further prospective validation. Research Sponsor: None.

Variable	OS (p-value)	PFS (p-value)
Low vs. High NLR	<0.0001	0.0002
High NLR + Combination	0.039	0.834
NLR Change (Baseline)	0.710	0.003

NLR values.

Pediatric patients with tenosynovial giant cell tumor: Real-world results from an observational registry.

Sydney Stern, Patrick McKenzie, Thomas Scharschmidt, Giacomo Giulio Baldi, Emanuela Palmerini, Sara Rothschild; TGCT Support/Life Raft Group, Wayne, NJ; Harvard University, Boston, MA; Nationwide Children's Hospital, Columbus, OH; Hospital of Prato, Prato, Italy; Osteoncology, Bone and Soft Tissue Sarcomas and Innovative Therapies - IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy; The Life Raft Group, Wayne, NJ

Background: Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive tumor originating in the synovial lining of the joint, bursa, and tendon sheath. Since TGCT typically impacts individuals 20-50 years of age, pediatric TGCT is ultra-rare. However, pediatric patients are often not included in clinical trials or prospective data. Real-world data are needed to understand the impact of TGCT on pediatric patients' quality of life and any differences between adults with TGCT. **Methods:** The TGCT Support Registry is an international, prospective registry initiated in 2022 by TGCT Support, a program of The Life Raft Group. The registry is the largest registry of patients with TGCT and records patient-reported demographic, pathologic, clinical information. This cross-sectional analysis presents data of patients ≤ 18 years of age at time of enrollment with Diffuse (D)-TGCT, Localized (L)-TGCT, or unknown subtype. **Results:** A total of 122 pediatric patients (9.5%) were included from a 1,278-patient registry (Table). Most patients were female (67.2%), had D-TGCT (73.0%), in the knee (83.6%), and a median age at diagnosis of 14.5 years. Symptoms reported were pain (94.3%), limited joint range of motion (89.3%), and swelling (84.4%). >50% of pediatric patients were initially misdiagnosed and were more likely to be misdiagnosed than adults (62.3% vs 49.9%, $p < 0.01$). 64.8% of pediatric patients were diagnosed by orthopedic surgeons, and 52.5% were diagnosed ≥1 years after symptom onset. Half of pediatric patients had joint aspirations to manage symptoms (47.5%) and non-steroidal anti-inflammatories were common (76.2%). Surgery was the predominant treatment modality and 61.5% reported that surgery occurred ≤ 3 months of diagnosis. Pediatric patients with D-TGCT underwent an average of 3.4 surgeries, compared to 1.8 surgeries for those with L-TGCT. 66.3% of pediatric patients with D-TGCT had ≥1 post-operative recurrence compared to 15.0% of L-TGCT pediatric patients. Most pediatric patients were referred to general orthopedic surgeons (80.3%), only a third consulted an oncology specialist, and 35.3% were also treated by pediatricians. Systemic therapies (i.e., imatinib, nilotinib, pexidartinib) were prescribed infrequently to pediatric patients with D-TGCT (17.2%). Pediatric patients reported that pain often interfered with daily activities and enjoyment of life. **Conclusions:** This real-world analysis highlights the significant disease burden of pediatric TGCT, as compared to adults, which severely affecting their quality of life. The reliance on surgical treatment and underuse of multidisciplinary care emphasizes the unmet need for provider education and treatment advancements tailored to this population. Greater efforts to develop systemic therapies specific to pediatrics are warranted to reduce recurrence rates and improve quality of life. Research Sponsor: None.

Characteristics of patients stratified by subtype (localized, diffuse, or unknown), including sex, age, region, location of disease, misdiagnosis, duration from symptom onset to diagnosis, average surgeries, recurrences, and use of systemic therapies.

	Diffuse (n=89, 73.0%)	Localized (n=20, 16.4%)	Unknown (n=13, 10.6%)	Total (N=122)
Female sex, n (%)	59 (66.3)	14 (70.0)	9 (69.2)	82 (67.2)
Median age at Diagnosis, years (range)	14 (3 - 17)	15 (4 - 17)	14.5 (7 - 15)	14.5 (3 - 17)
Median age at Enrollment, years (range)	16 (4-18)	17 (6-18)	15 (10-18)	16 (4-18)
Located in the US, n (%)	47 (52.8)	11 (55.0)	4 (30.8)	62 (50.8)
Location of disease, n (%)				
Knee	76 (85.4)	16 (80.0)	10 (76.9)	102 (83.6)
Hip	8 (9.0)	4 (20.0)	1 (7.7)	13 (10.7)
Ankle	5 (5.6)	0 (0.0)	0 (0.0)	5 (4.1)
Other[a]	0 (0.0)	0 (0.0)	2 (15.4)	2 (1.6)
Misdiagnosis, n (%)	56 (62.9)	10 (50.0)	10 (76.9)	76 (62.3)
Time from Symptom Onset to Diagnosis, n (%)				
<12 months	42 (47.1)	8 (40.0)	4 (30.8)	54 (44.3)
12–24 months	24 (27.0)	5 (25.0)	3 (23.1)	32 (26.2)
25–60 months	14 (15.7)	4 (20.0)	3 (23.1)	21 (17.2)
>60 months	6 (6.7)	3 (15.0)	2 (15.4)	11 (9.0)
Diagnosed during Surgery	3 (3.4)	0 (0.0)	1 (7.7)	4 (3.3)
Average surgeries, (SD)	3.4 (2.8)	1.8 (1.5)	1 (1.2)	2.9 (2.5)
Median	2	1	1	2
Systemic Therapy,	20 (22.5)	0 (0.0)	1 (7.7)	21 (17.2)
Checkall that apply				
Pexidartinib	7 (7.9)	0 (0.0)	1 (7.7)	8 (7.4)
Imatinib	12 (13.5)	0 (0.0)	0 (0.0)	12 (9.8)
Nilotinib	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.8)
Local Recurrences, n (%)				
Yes	59 (66.3)	3 (15.0)	4 (3.8)	66 (54.1)
1 Recurrence	19 (21.3)	2 (10.0)	1 (7.7)	22 (18.0)
≥ 2 Recurrences	40 (44.9)	1 (5.0)	3 (23.1)	44 (36.1)
No	30 (33.7)	17 (85.0)	9 (69.2)	56 (45.9)
I have not had surgery	12 (13.5)	2 (10.0)	5 (38.5)	19 (15.6)
I am unsure	8 (9.0)	4 (20.0)	1 (7.7)	13 (10.7)

11545 Poster Session

IMM2510, an anti-PD-L1/VEGF bispecific antibody fusion protein, in patients with R/R STS: A phase Ib expansion study.

Haiyan Xu, Shegan Gao, Ruinuo Jia, Weifeng Liu, Zhen Huang, Bin Li, Jian Zhang, Wang Ma, Suxia Luo, Weitao Yao, Binghao Li, Xiangdong Cheng, Zhengbo Song, Xi Xi Wu, Hao Pang, Deqiang Jing, Liyun Yang, Qiying Lu, Wenzhi Tian, Xichun Hu; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, Shanghai, China; The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China; Beijing Jishuitan Hospital, Capital Medical University, Beijing, China; Xiangya Hospital of Central South University, Changsha, China; Fudan University Shanghai Cancer Center, Shanghai, China; The First Affiliated Hospital of Zhengzhou University, Henan, China; Henan Cancer Hospital, Zhengzhou, China; Henan Provincial Cancer Hospital, Zhengzhou, China; The Second Affiliated Hospital of Zhejiang University School of Medicine, Hzhou, Zhejiang, China; Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China; Zhejiang Cancer Hospital, Hangzhou, China; Cancer Hospital of Dalian University of Technology, Liaoning Cancer Hospital & Institute, Liaoning, China; ImmuneOnco Biopharmaceuticals (Shanghai) Inc., Shanghai, China

Background: IMM2510 is a novel bispecific antibody fusion protein targeting PD-L1 and VEGF. The results of dose-escalation phase were previously reported. Here, we report further efficacy and safety of soft tissue sarcoma patients in cohort expansion stage. **Methods:** IMM2510-01 was a phase I, multicenter, open-label study designed to evaluate the safety, efficacy, recommended phase II dose (RP2D), and pharmacokinetics (PK) of IMM2510 monotherapy (NCT05972460). Dose escalation stage completed and administration of IMM2510 at 20mg/kg, Q2W was selected for cohort expansion. Advanced soft tissue sarcoma patients after prior systemic treatment failure were enrolled, including these with alveolar soft part sarcoma (ASPS), undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma (LMS) and synovial sarcoma (SS) patients. The primary endpoint was safety, tolerability and investigator assessed ORR. **Results:** As of 24 Dec 2024, 29 STS patients were treated in cohort expansion stage, including 10 with ASPS, 5 with UPS, 8 with LMS, 5 with SS and 1 with other STS subtypes. The median age was 45 and most patients (89.7%) were ECOG PS 1. The median number of prior systemic treatment was 2. Most patients (96.6%) experienced treatment-related adverse events (TRAEs), of which 3 (10.3%) were ≥ Grade 3. The most common TRAEs of any grade was infusion-related reaction (IRR) (37.9%), platelet decreased (31%) and AST increased (27.6%). TRAE of ≥ Grade 3 was reported in 3 patients, including 1 platelet decreased, 1 transaminase increased and 1 hypoaesthesia. No TRAE leading to treatment discontinuation was observed. Of 27 efficacy-evaluable STS patients, ORR was 7.4% and DCR was 55.6%. 2 PR and 4 SD with tumor shrinkage were observed. PRs were noted in the UPS and LMS cohorts, with an ORR of 20% and 14.3%, and a DCR of 60% and 42.9%, respectively. The DOR was not reached in UPS and 3.68 months in LMS. The study is ongoing. **Conclusions:** IMM2510 monotherapy demonstrated active anti-tumor activity in R/R STS patients with tolerable toxicity. Clinical trial information: NCT05972460. Research Sponsor: None.

11546 Poster Session

A pilot study of Janus kinase 1 (JAK1) inhibitor itacitinib for treatment-refractory sarcomas: Leiomyosarcoma cohort.

Michael J. Wagner, Lee D. Cranmer, Elizabeth Trice Loggers, Roxanne Moore, Shannon Hill, Anirudh Goyal, Munther Baroudi, Niall Morin, Rylee Johnson, Kimberly Smythe, Lauri Aicher, Cecilia Yeung, Seth Pollack; Dana-Farber Cancer Institute, Boston, MA; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Clinical Research Division, Fred Hutchinson Cancer Center/Division of Hematology and Oncology, University of Washington, Seattle, WA; University of Washington, Seattle, WA; University of Washington/Fred Hutch Cancer Center, Seattle, WA; Brigham and Woman's Hospital, Boston, MA; Seattle Cancer Care Alliance, Seattle, WA; Fred Hutch Cancer Center, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; Fred Hutchinson Cancer Center, Seattle, WA; Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL

Background: Sarcomas are a heterogenous group of mesenchymal tumors. Although variable, many sarcoma subtypes have a high proportion of infiltrating macrophages in their immune microenvironment. The JAK/STAT pathway is involved in immune cell regulation and may play a role in tumor immune resistance. Janus kinase 1 (JAK1) shifts tumor associated macrophages (TAM) to an inhibitory M2 phenotype. Inhibition of this pathway could improve anti-tumor immunity. **Methods:** This is an open-label, single agent, pilot study of the JAK1 inhibitor itacitinib in subjects with metastatic or advanced treatment-refractory sarcomas susceptible to immune infiltration by TAM (NCT03670069). Patients (pts) age 18 and older were enrolled in four cohorts: leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma (UPS) and related subtypes, synovial sarcoma and myxoid/round cell liposarcoma (MRCL), and chondrosarcoma. Itacitinib was given orally, 300 mg once daily, in a 28-day cycle. Primary endpoint was to assess changes in the macrophage population with itacitinib. Secondary endpoints included objective response rate using RECIST v1.1 criteria, progression free survival (PFS) at 3- and 6- months, and overall survival (OS) at 12-months. Response assessments were performed after cycle 2, and every other cycle thereafter. Research biopsies for pharmacodynamic markers were collected at baseline prior to C1D1 and prior to C3D1. Multiplex immunohistochemistry (mIHC) and transcriptomic analysis using Nanostring were performed on pre-treatment and on-treatment tumor specimens. We report the results from the LMS cohort. **Results:** 8 pts with LMS enrolled. OS rate at 12 months for the LMS cohort was 100%, median OS for LMS was 23 months. PFS rate at 3 months and 6 months for LMS was 75% and 38%, respectively. No objective responses by RECIST v1.1 were documented. 7/8 (87.5%) of pts with LMS had stable disease as best response. 7/8 LMS pts had paired tumor biopsies pre- and on-treatment. As expected, *STAT1* was significantly downregulated in on-treatment whole tumor lysates. Other genes that were significantly downregulated with itacitinib treatment were *CCR5, NFKB1, C1QB, CIITA, FCGR3A/B, CXCL10, and MAPKAPK2*. On mIHC, there was a general trend of decreased immune cell tumor infiltration (CD3, CD4, CD8, CD163, FOXP3, CD14, CD206) in on-treatment samples compared to pre-treatment samples, though differences were not statistically significant. **Conclusions:** Itacitinib demonstrated durable disease control in patients with LMS and warrants further study in this subtype. While our analysis of markers on paired biopsy samples does not suggest that immunotherapy combinations with itacitinib are likely to be successful for LMS, a more thorough analysis will be presented at the meeting as this data may still suggest potent combination therapies. Clinical trial information: NCT03670069. Research Sponsor: Incyte.

11547 Poster Session

Gamma secretase inhibitors and desmoid fibromatosis: Lessons from a real world, comprehensive genomic study of desmoids and *CTNNB1/APC* mutated soft tissue tumors.

Steven Christopher Smith, Kieran Sweeney, Andrew Elliott, Andrew Stewart Poklepovic, Anna Miller, Gretchen Hubbard, Matthew James Oberley, Jerry J. Lou, David J Papke Jr., Gina Z. D'Amato, Mark Gordon Evans; Virginia Commonwealth University School of Medicine, Richmond, VA; Caris Life Sciences, Irving, TX; Caris Life Sciences, Phoenix, AZ; Massey Cancer Center, Virginia Commonwealth University, Richmond, VA; CARIS Life Sciences, Irving, TX; UCI Health, Orange, CA; Brigham and Women's Hospital, Boston, MA; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Recently, first-in-class FDA approval was granted in the U.S. for use of the gamma secretase inhibitor (GSI), nirogacestat, for adults with progressive desmoid fibromatosis. In tandem, the unpredictable clinical behavior of desmoids, which ranges from local aggression to regression, raises consideration of whether diagnostic and molecular variability underlie their varying biological potential. With an aim to understand both, and to explore the potential for biomarkers for GSI therapy selection, prediction, and prognosis, we performed a retrospective review of comprehensive genomic profiling and histology of desmoids and other soft tissue tumors harboring *CTNNB1* or *APC* mutations. **Methods:** Using real-world reference laboratory database of tumors submitted for clinical genomic assessment (Caris Life Sciences), we queried for samples with a diagnosis of desmoid fibromatosis, or for other neoplasms of soft tissue origin harboring *CTNNB1* or *APC* mutations. Samples underwent next-gen sequencing of (whole exome) to identify gene variants/copy number alterations and of RNA (whole transcriptome) for expression and fusion profiling. Findings were correlated with available clinical data and whole slide image histologic review. **Results:** We identified 74 tumors submitted as desmoid fibromatosis, of which 80% harbored *CTNNB1* and 15% harbored *APC* pathogenic or likely pathogenic variants. *CTNNB1* variants included codon 41 (58%), codon 45 (41%), and ubiquitin motif codon 36 (1%), while 91% of APC variants detected were in exon 16. Recurrent co-alterations were rare, involving *MUTYH* (heterozygous G396D) in 2 samples, and TMB-High (≥10 mutations/Mb) present in 3. Notably, 4 "desmoids" (5%) lacked characteristic mutations, one of which harbored *COL1A1::USP6* fusion, reclassified as nodular fasciitis. Among 76 soft tissue tumors diagnosed as other entities at analysis but found to harbor CTNNB1/APC mutations, 6 (all limited core biopsies), could be confidently reclassified as desmoids. The remaining 70 *CTNNB1/APC* mutant neoplasms were diverse, including synovial sarcoma (11%) and rhabdomyosarcoma (10%). **Conclusions:** Correlation of genomics and histopathology may allow identification of other tumor types misclassified as desmoid fibromatosis. Conversely, genomic correlation facilitated recognition of additional desmoids among tumors submitted with other diagnoses. The striking lack of secondary mutations seen in this large cohort with comprehensive DNA sequencing implies that other mechanisms explain and could predict their variable behavior, for which we are exploring paired transcriptome profiling data. Finally, subsets of diverse, other soft tissue neoplasms harbor *CTNNB1* or *APC* mutations, which may have implications for the design of future biomarker-selected Phase II basket trials. Research Sponsor: None.

11548 Poster Session

The global, regional, and national burden of soft tissue sarcomas and other extraosseous sarcomas, 1990-2021: A systematic analysis for the Global Burden of Disease study 2021.

Venkatraman Radhakrishnan, Nickhill Bhakta, Lisa Force, Carlos Rodriguez-Galindo, Paola Friedrich, Franny Dean, Kayleigh Bhangdia, Acheson Alistair, Kelly Compton, Lee Deitesfeld, Weijia Fu, Brian Gaw, James Harvey, Jonathan Kocarnik, Dan Lu, Louise Penberthy, Miranda May, Alyssa Pennini, Natalie Pritchett, Rixing Xu; Cancer Institute (WIA), Chennai, India; St. Jude Children's Research Hospital, Memphis, TN; University of Washington School of Medicine, Seattle, WA; Department of Global Pediatric Medicine, St. Jude Children's Research Hospital, Memphis, TN; Institute for Health Metrics and Evaluation, Seattle, WA; Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA

Background: Soft tissue and other extraosseous sarcomas (STS) are a diverse group of cancers whose global burden have not been comprehensively reported. This study aims to analyze the burden of STS across the lifespan globally, regionally, and by Socio-demographic Index (SDI) using the Global Burden of Diseases, Injuries, and Risk Factors Study 2021 (GBD 2021) estimates. **Methods:** The incidence, mortality, and disability-adjusted life-years (DALYs) due to STS from 1990 to 2021 were estimated using GBD 2021 methods. Funding for this research came from the Bill & Melinda Gates Foundation and American Lebanese Syrian Associated Charities. **Results:** In 2021, 96,200 (83,400-116,000) new cases of STS occurred globally (males: 52,300 [43,200-68,500], females: 43,900 [38,500-51,400]) and the global age-standardized incidence rate (ASIR) was 1.2 (1.0-1.4) per 100,000 person-years (males: 1.3 [1.1-1.7], females: 1.0 [0.9-1.2]). Among the pediatric population, the incidence rate was highest in the 0-4 age group, while in adults the incidence rate was highest in the 95+ age group. Deaths from STS were estimated to be 50,200 (43,200-61,300) globally (males: 27,200 [22,100-36,500], females: 23,000 [19,900-27,500]), with an age-standardized mortality rate (ASMR) of 0.6 (0.5-0.7) (males: 0.7 [0.6-0.9], females: 0.5 [0.5-0.6]). STS was responsible for 1,680,000 (1,430,000-2,120,000) DALYs in 2021 (males: 916,000 [732,000-1,31,000], females: 762,000 [654,000-947,000]). The global age-standardized DALY rate in 2021 was 20.5 (17.5-26.1) (males: 23.0 [18.3-33.0], females:18.3 [15.7-23.0]). Notably, in 2021, the low SDI quintile exhibited the highest ASMR of 0.9 (0.7-1.4) and age-standardized DALY rate of 33.4 (25.6-50.2). In contrast, the high SDI quintile had the highest ASIR of 2.0 (1.9-2.2). The ASIR remained stable globally between 1990 and 2021, whereas the ASMR and age-standardized DALY rates declined. **Conclusions:** Variations in the burden of STS were evident across different SDI levels. These findings offer insights into the distribution and discrepancies in STS burden on a global scale, which can aid policy efforts to alleviate the suffering caused by these cancers. Research Sponsor: None.

11549 Poster Session

Clinicopathologic features and outcomes of follicular dendritic cell sarcoma with or without Castleman disease: A large retrospective cohort analysis.

Yoshito Nishimura, Dongni Yi, Steven Ian Robinson, Ronald S. Go, Karen Rech, Angela Dispenzieri; Division of Hematology and Oncology Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN; Division of Medical Oncology, Mayo Clinic, Rochester, MN; Division of Hematology, Mayo Clinic, Rochester, MN

Background: Follicular dendritic cell sarcoma (FDCS) is a rare neoplasm with a subset associated with unicentric Castleman disease (UCD). However, the impact of CD association on clinicopathologic features and survival outcomes remains unclear. This study aims to elucidate differences in disease characteristics and outcomes in FDCS with and without CD to guide future research and clinical practice. **Methods:** We retrospectively analyzed 41 FDCS patients seen at Mayo Clinic between January 2000 and December 2024. Patients were categorized into CD-related (n = 9) and FDCS-only (n = 32) groups. Demographic, clinical, pathological, and survival data were compared. Kaplan-Meier survival analyses were used to evaluate overall survival (OS) and progression-free survival (PFS). Epstein-Barr virus-associated inflammatory FDCS were excluded. **Results:** The CD-related group was younger at diagnosis (46.0 vs. 58.0 years, p = 0.041). Among those with CD-related FDCS, FDCS was diagnosed concurrently as CD in 6/9 (66.7%) and after the diagnosis of CD in 3/9 (33.3%). The FDCS-only patients were more likely to have extranodal disease (71.9% vs. 22.2%) and to have metastasis (62.5% vs 22.2%). One CD-related FDCS patient had paraneoplastic pemphigus. Among 11 patients with next-generation sequencing (NGS) results, 9 had pathogenic mutations. The most common pathogenic mutations included CDKN2A, CDKN2B, and TRAF3 copy number losses. Surgery was the preferred first-line intervention in FDCS-only and CD-related FDCS groups (19/32, 59.4% vs. 6/9, 66.7%). Eight out of 32 (25.0%) of the FDCS-only group received chemotherapy at first-line, most commonly Gemcitabine/Docetaxel or Adriamycin/Ifosphamide. While Gemcitabine/Docetaxel was the most preferred in the second line, different regimens were pursued in the third and later lines of therapy, including Pembrolizumab, Pazopanib, and stem cell transplant. Five out of 6 patients in the CD-related FDCS group received either adjuvant radiation or chemotherapy, which led to complete remission during the follow-up periods. The median follow-up was 22.4 months for the whole population. There was a trend for better OS and PFS among CD-related FDCS patients. The respective 2-year OS rates were 100% and 66.7%, and 2-year PFS rates were 57.1% and 43.1% for CD-related FDCS and FDCS-only patients, respectively. **Conclusions:** This study provides novel insights into clinicopathologic differences and survival trends for FDCS. Our data would suggest a less aggressive disease course among CD-related FDCS, which implies the need for different treatment strategies for CD and non-CD-related FDCS. Further research is warranted to elucidate these mechanisms, such as multi-omic analysis on benign FDC proliferation in the microdissected UCD areas and the adjacent FDCS cells to determine factors associated with progression to sarcoma. Research Sponsor: None.

11550 Poster Session

Molecular-genetic characteristics of soft tissue sarcomas associated with the development of chemotherapy resistance.

Anastasia Alekseevna Tararykova, Timur Fetisov, Polina Shtompel, Sofya Khazanova, Ekaterina Trapeznikova, Maxim Menyailo, Alexander Ikonnikov, Elena Kopantseva, Anastasia Korobeynikova, Beniamin Bokhyan, Marianna G. Yakubovskaya, Kirill I. Kirsanov; Federal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russian Federation; Research Institute of Molecular and Cellular Medicine, Peoples' Friendship University of Russia (RUDN University), Moscow, NA, Russian Federation

Background: The development of resistance is the one of the reason for ineffective treatment of soft tissue sarcomas (STSs). The search for new molecular-biological targets, both for the personalized selection of novel targeted drugs and for predicting chemoresistance of STSs to individual antitumor agents and their combinations, is a pressing task. **Methods:** In this study, an experimental in vitro chemoresistance analysis, whole-genome sequencing, and single-cell sequencing of tumors in patients (N = 9) with undifferentiated pleomorphic sarcomas were performed. Chemotherapy resistance indices were determined for the obtained samples. **Results:** Whole-genome DNA sequencing yielded data on the type and frequency of somatic mutations in undifferentiated pleomorphic sarcomas, and driver genes of carcinogenesis were identified, among which the most frequently occurring were FCGBP, PARP4, TP53, RGPD3, PDE4DIP, and RB1. Correlations between the presence of genetic alterations and the response to chemotherapy in the in vitro test were sought. Thus, in samples resistant to the combination of doxorubicin and ifosfamide, the presence of mutations in the PEG3, USP8, NT5C3A, and WAS genes was characteristic. Bioinformatic analysis of single-cell transcriptome sequencing data, aimed at characterizing the population composition and transcriptomic landscape of undifferentiated pleomorphic sarcoma cells, revealed 15 normal and 8 tumor cell populations. Among the populations of normal cells, the following clusters were identified: M2 and M1 macrophages, T-cells, matrix-remodeling fibroblasts and myofibroblasts, monocytes, stromal cells, endothelial cells, and osteoblasts. Among tumor cells, clusters of proliferating cells, hypoxic cells, matrix-interacting cells, and tumor cells with a stem-like phenotype were identified. The most common clusters in all samples were M2 macrophages, endothelial cells, and one of the clusters of tumor cells interacting with the matrix. Comparison of the expression profiles of cells from patients with different responses to chemotherapy allowed identification and characterization of clusters associated with chemosensitivity and chemoresistance. These included clusters of macrophages, tumor cells, fibroblasts, and endothelial cells. In addition, genes common to all clusters associated with resistant samples were identified (ARGLU1, JUND, TNNT3, RHOB, CCNL2, LENG8, LUC7L3, KLF9, RSRP1, RNF213, SERPINE1, CDK5RAP3). **Conclusions:** The data obtained in this study will expand the understanding of the pathogenesis of undifferentiated pleomorphic sarcomas and the mechanisms underlying their development of chemotherapy resistance. In the future, this will serve as the basis for creating a test system to evaluate the expression levels of genes whose activation/repression is associated with the development of drug resistance in STSs. Research Sponsor: None.

11552 Poster Session

Overall survival from the open label phase 2 trial of palbociclib in patients with advanced well differentiated/dedifferentiated liposarcoma.

Olayode Babatunde, Gary K. Schwartz, Mary Louise Keohan, Sandra P. D'Angelo, Mrinal M. Gounder, Ping Chi, Cristina R. Antonescu, Jonathan Landa, Kenneth Seier, Li-Xuan Qin, Aimee Marie Crago, Samuel Singer, William D. Tap, Mark Andrew Dickson; Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY; Case Western Reserve University, Cleveland, OH; Memorial Sloan Kettering Cancer Center, New York, NY; Sarcoma Medical Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Liposarcomas (LPS) are among the most common soft tissue sarcoma subtypes. Well-differentiated (WD) and dedifferentiated (DD) LPS are characterized by CDK4 and MDM2 amplification. Both subtypes have variable sensitivity to chemotherapy. However, effective systemic treatment options remain limited for unresectable or metastatic disease. Our group previously reported two phase 2 trials of the CDK4/6 inhibitor (CDK4/6i) palbociclib (PD0332991) in advanced WD/DD LPS, which established proof-of-concept for targeting CDK4 in this disease. Palbociclib demonstrated prolonged progression-free survival (PFS) and was included in the NCCN Compendium for LPS. However, prospective data on overall survival (OS) in this population remain limited. We now report OS analysis approximately 8.5 years after the last patient was enrolled. **Methods:** Patients with advanced WD/DD LPS were enrolled in two non-randomized phase 2 trials of palbociclib: cohort A received 200 mg daily for 14 days on a 21-day cycle, while cohort B received 125 mg daily for 21 days on a 28-day cycle. Survival outcomes were analyzed using Kaplan-Meier methods, and baseline factors were evaluated for association with PFS and OS. Subsequent anti-cancer therapies, including surgery and systemic treatments, were recorded and analyzed. **Results:** Among 90 enrolled patients, 88 were evaluable for PFS. Median follow-up was 17 months for cohort A and 21 months for cohort B. Updated median PFS was 18.2 weeks (95% CI: 17.7–36.4 weeks) in cohort A and 18.8 weeks (95% CI: 12–23.4 weeks) in cohort B. Median OS was 25.6 months (95% CI: 17.2–40.0 months) in cohort A and 24.1 months (95% CI: 17.5–38.4 months) in cohort B. Across both cohort, patients with pure WD histology were underrepresented, comprising 15 of the 90 patients. Patients with pure WD histology demonstrated longer PFS compared to patients with DD or WD/DD histology (HR: 0.55; 95% CI: 0.30–0.99). However, no significant difference in OS was observed between histologic groups (HR: 0.64; 95% CI: 0.35–1.16). Surgery was performed on 35 patients (39%) post-palbociclib, of which 5 patients had pure WD histology. Analyses on subsequent therapies, including surgery and systemic treatments, will be presented at the meeting. **Conclusions:** This study provides updated long-term outcomes for palbociclib in advanced WD/DD LPS. Palbociclib demonstrated consistent PFS and OS across dosing regimens, offering a tolerable alternative to chemotherapy for patients who may not be candidates for cytotoxic agents. While PFS and OS outcomes remain modest, these data reaffirm the role of CDK4/6i in the management of this disease and underscore the need for novel therapeutic strategies. Future efforts should focus on biomarker-driven approaches and combination therapies to optimize outcomes in this challenging disease. Clinical trial information: NCT01209598. Research Sponsor: Kristen Ann Carr Fund; Nicholls-Biondi Fellowship.

11553 Poster Session

Clinical activity of immune checkpoint blockade in advanced perivascular epithelioid cell neoplasms (PEComas): A retrospective single center study.

Daniel Reinhorn, Sandra P. D'Angelo, William D. Tap, Ciara M. Kelly, Mrinal M. Gounder, Mary Louise Keohan, Michael Vincent Ortiz, Sujana Movva, Evan Rosenbaum, Aimee Marie Crago, Samuel Singer, Minsi Zhang, Kaled M. Alektiar, Mark Andrew Dickson; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal neoplasms with limited therapeutic options. While therapies targeting the mTOR pathway have shown promise, with nab-sirolimus being the first FDA-approved treatment for this histology, most patients will eventually progress. The role of immune checkpoint inhibitors (ICIs) remains poorly defined in these patients. Here, we present a retrospective analysis of PEComa patients treated with ICIs at Memorial Sloan Kettering Cancer Center (MSKCC). **Methods:** We retrospectively reviewed all patients with histologically confirmed PEComa treated with ICIs at MSKCC between 2016 and 2024. Patient demographics, disease characteristics, molecular profiles, treatment details, and clinical outcomes were collected. Endpoints included real-world progression-free survival (rwPFS), overall survival (OS), time on treatment (ToT) and response rate. **Results:** Thirteen patients with advanced PEComa received ICIs. The median age was 62 years (Range: 16-87), with 62% female patients. Primary tumor sites included uterus (n = 2), gastrointestinal tract (n = 4), soft tissue/extremities (n = 3), thyroid (n = 1), bladder (n = 1), renal (n = 1), and liver (n = 1). The most common molecular alterations identified were TFE3 fusions (23%), TSC1/TSC2 mutations (15%), TP53 alterations (46%) and ATRX mutations (46%). Patients received a median of 2 lines of previous therapies (range 1-6), with all patients receiving mTOR inhibitors (nab-Sirolimus in 46%). Most patients (78%) had previously received chemotherapy (gemcitabine and/or anthracycline, 54% each). ICIs included pembrolizumab (n = 5), nivolumab (n = 2), nivolumab-ipilimumab (n = 4), pembrolizumab-lenvatinib (n = 1) and nivolumab-bempegaldesleukin (n = 1). Median ToT was 1.6 months (95% CI: 0.9-NE) with 31% (95% CI 14-70%) remaining on treatment at 3 months. Median rwPFS was 3 months (95% CI: 1.4-NE) with a 6-month PFS of 38% (95% CI: 19-76%). Median OS was 26 months (95% CI: 4.13-NE) with a 12-month OS of 59% (95% CI: 37-95%). Partial responses were observed in three patients (23%), with two achieving durable responses exceeding 18 months (one on pembrolizumab and one on nivolumab-ipilimumab). These long-term responders subsequently underwent local interventions for oligoprogressive disease and remained progression-free at last follow-up. Molecular analysis of responders showed distinct profiles: one had TFE3 fusion, another had TP53 deletion and RB1 mutation, while the third had NOTCH1 and FLT4 mutations. **Conclusions:** The observed response rate of 23%, including two durable responses, suggests that ICIs may be an effective treatment option for a subset of PEComa patients, regardless of molecular profile. Further studies to identify predictive biomarkers and optimal sequencing with mTOR inhibitors and other therapies are warranted. Research Sponsor: None.

11554 Poster Session

An update on the results of IBI110 (anti-LAG-3 antibody) plus sintilimab (anti-PD-1 antibody) in patients with advanced alveolar soft part sarcoma.

Zhichao Tan, Jiayong Liu, Yan Wu, Zhengfu Fan, Chujie Bai, Ruifeng Xue, Shu Li, Tian Gao, Lu Zhang, Mengmeng Liu, Xinyu Wang; Department of Bone and Soft Tissue Tumor, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Department of Pathology, Peking University Cancer Hospital & Institute, Beijing, China; Department of Bone and Soft Tissue Tumor, Peking University Cancer Hospital, Beijing, China; Department of Bone and Soft Tissue Tumor, Peking University Cancer Hospital & Institute, Beijing, China; Peking University Cancer Hospital, Beijing, China; Peking University Cancer Hospital & Institute, Beijing, China

Background: At the 2024 ASCO conference, we reported preliminary results on the efficacy and safety of IBI110 (anti-LAG-3 antibody) combined with sintilimab (anti-PD-1 antibody) in advanced alveolar soft part sarcoma (ASPS), which demonstrated an overall response rate (ORR) of 48.1%, including three complete responses (CRs). Here, we provide updated results from this single-arm, phase II trial. **Methods:** Eligible patients with metastatic or unresectable ASPS were assigned to two cohorts: cohort A (immune checkpoint inhibitor [ICI]-naïve, defined as no prior exposure to anti-PD-1/PD-L1/CTLA-4 antibodies) and cohort B (ICI-failed, defined as imaging-confirmed progression following anti-PD-1/PD-L1 therapy). Patients received IBI110 (200 mg) plus sintilimab (200 mg) intravenously every three weeks (Q3W). Primary endpoints were ORR and progression-free survival (PFS), assessed by investigators per RECIST v1.1, as well as safety. Secondary endpoints included overall survival (OS) and safety profile. **Results:** A total of 28 patients were enrolled (57.1% male; median age: 30.5 years; ECOG performance status 0: 100%; stage IV: 100%), with 20 patients in cohort A and 8 in cohort B. Responses were evaluable in 27 patients. The ORR was 51.8% across the entire population, including 4 CRs and 8 partial responses (PRs) in cohort A, and 2 PRs in cohort B. As of January 8, 2025, the median follow-up duration was 21.3 months (95% CI: 11.5–29.8). Median PFS and OS were not reached in the overall population (see Table). Treatment-related adverse events (TRAEs) occurred in all patients, with grade ≥3 TRAEs observed in 10 (35.7%) patients. Four TRAEs led to treatment discontinuation, including hemoptysis (n=2), type 1 diabetes mellitus (n=1), and encephalitis (n=1). No TRAE-related deaths were reported. Following discontinuation of LAG-3 antibody production in July 2024, patients achieving CR were advised to discontinue therapy, while those with PR or stable disease (SD) transitioned to sintilimab monotherapy. Notably, no disease progression was observed among these patients, including two who were previously resistant to sintilimab. Tumor microenvironment analysis in 17 patients (10 responders and 7 non-responders) revealed significantly higher LAG-3 density in responders compared to non-responders (P=0.021). **Conclusions:** The combination of IBI110 and sintilimab demonstrated promising efficacy in both ICI-naïve and ICI-failed advanced ASPS with an acceptable safety profile. The durable restoration of ICI efficacy persisted despite the discontinuation of combination therapy. LAG-3 expression may serve as a predictive biomarker for response to anti-LAG-3 therapy in ASPS. Research Sponsor: None.

Survival analysis.

Cohort	PFS (m)	OS (m)
A	Not reached	Not reached
B	14.9	25.4
Whole population	Not reached	Not reached

PFS: progression-free survival; OS: overall survival.

11555 Poster Session

Comprehensive molecular analysis of phase IB/II trial of durvalumab plus doxorubicin combination in patients with advanced soft-tissue sarcoma.

Hyo Song Kim, Kum-Hee Yun, Nam Suk Sim, Su-Jin Shin, Young Han Lee, Wooyeol Baek, Yoon Dae Han, Sung Hyun Kim; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Department of Otorhinolaryngology, Severance Hostpital, Yonsei University College of Medicine, Seoul, South Korea; Department of Pathology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; Department of Radiology, Yonsei University College of Medicine, Seoul, South Korea; Yonsei University College of Medicine, Seoul, South Korea; Yonsei Cancer Center, Seoul, South Korea

Background: We conducted an open-label, phase IB/II study to determine the activity and safety of the standard-of-care, doxorubicin in combined with the anti-PD-L1 immune checkpoint inhibitor, durvalumab, in patients with anthracycline-naïve soft tissue sarcoma (STS) and identified patients who would likely benefit from combination treatment. **Methods:** In this phase IB/II trial (NCT03798106), we enrolled patients with metastatic and/or recurrent STS had not received anthracycline chemotherapy and PD-L1/PD-1 inhibitor. Tumor biopsies were obtained from all patients prior to treatment for targeted sequencing, RNA sequencing, and Opal multiplexed immunofluorescence staining. **Results:** No DLTs were observed during the phase II and recommended phase II dose was defined at doses of 75/m^2 doxorubicin and proceed the phase II part. Of 41 evaluable patients, an objective response rate of 31.7% and the median progression free survival was 8.2 months (95% CI, 7.3-9.0) and median overall survival was 24.1 months (95% CI, 7.6-40.3). In the prespecified genomic analysis, using a multivariate Cox proportional regression model with clinical factors in combined with PD-1 cell density and signaling pathways, genetic alterations in RTK/RAS (HR 6.446, [95 % CI, 1.934-21.486]; P=0.002) and PD-1 density (HR 0.214, [95 % CI, 0.071=0.649]; P=0.006) were identified as the independent predictors of PFS. High PD-1 tumors without RTK/RAS pathway alteration had longer PFS (16.9 months) than the others (7.4 months for RTK/RAS alteration or PD-1 high, 1.0 months for RTK/RAS pathway alteration and PD-1 low group, P<0.001). In the gene set analysis, antigen processing and presentation, interferon alpha response, and interferon gamma response showed significantly higher scores in PD1 high without RTK/RAS pathway alteration. **Conclusions:** Durvalumab combined with doxorubicin demonstrated promising efficacy in an unselected STS cohort, with a manageable toxicity profile. In exploratory correlative analysis, we identified potential role of RTK/RAS signaling and PD-1 expression as independent predictors for the efficacy, although further investigations are needed. Clinical trial information: NCT03798106. Research Sponsor: None.

11556 Poster Session

Multicenter phase II study of anlotinib and toripalimab in patients with advanced soft tissue sarcoma (STS) and bone sarcoma (BS).

Xing Zhang, Qiuzhong Pan, Peng Zhang, Lihong Zhang, Hui Li, Ruiqing Peng, Bushu Xu; Melanoma and Sarcoma Medical Oncology Unit, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; Melanoma and Sarcoma Medical Oncology Unit, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-Sen University, Guangzhou, China; Department of Bone and Soft Tissue, the Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Department of Gastrointestinal Medical Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China

Background: This multicenter phase II study aims to evaluate the efficacy and safety of anlotinib combined with toripalimab in the treatment of patients (pts) with advanced STS or BS. **Methods:** Pts with advanced STS or BS, 14-70 years, at least one measurable tumor lesion per RECIST 1.1 and failure or intolerance of standard systemic therapy, or no standard treatment existed, are eligible. Pts with alveolar soft-part sarcoma (ASPS) and clear cell sarcoma (CCS) can be included as the first-line therapy. Anlotinib (12 mg/d, po, d1-14) and toripalimab (240mg, IV, d1) would be administered every 3 weeks. The primary endpoint was investigator-assessed objective response rate (ORR). The secondary endpoints include disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety using NCI-CTCAE v4.03. **Results:** Between March, 2020 and November, 2024, 70 pts were enrolled, of whom 68 were evaluable for the efficacy analyses. The STS subtypes mainly included synovial sarcoma (SS, 15.7%), rhabdomyosarcoma (RMS, 8.6%), extraskeletal Ewing's sarcoma (EES, 7.1%), epithelioid sarcoma (EpS, 7.1%), leiomyosarcoma (LMS, 7.1%), ASPS (5.7%), liposarcoma (5.7%), undifferentiated sarcoma (5.7%) and others (31.4%). The BS subtypes included 2 (2.9%) osteosarcoma and 2 (2.9%) chondrosarcoma. With a median follow up of 29.1 months, partial response occurred in 19 pts: 4 with SS, 3 with ASPS, 2 with LMS, 2 with EpS, 2 with inflammatory myofibroblastic tumor, and one patient each with RMS, EES, undifferentiated sarcoma, CCS, malignant peripheral nerve sheath tumor, or desmoplastic small round cell tumor. The ORR and DCR for the entire cohort were 27.9% and 86.8%, respectively. The median PFS was 7.0 months (95% CI: 4.2-9.8). The median OS was 23.5 months (95% CI: 9.2-37.8). For the 64 efficacy-evaluable STS cohort, the ORR was 29.7% and the median PFS was 8.1 months (95% CI: 4.7-11.5). Most of the treatment-related adverse events were mild (grade 1-2). The most common grade 3/4 adverse events (AE) were hypertension (15.7%), hand-foot syndrome reaction (12.9%), and hypertriglyceridemia (7.1%). **Conclusions:** The combination of anlotinib and toripalimab showed good anti-tumor activity and durable efficacy in advanced STS patients, with acceptable toxicity. Clinical trial information: NCT04172805. Research Sponsor: None.

11557 Poster Session

Change in T2-weighted signal intensity, change in tumor volume, and exposure-response analysis in the RINGSIDE phase 2 study of varegacestat in patients with desmoid tumors.

Mrinal M. Gounder, Bernd Kasper, Rashmi Chugh, Arun S. Singh, Brian Andrew Van Tine, Vladimir Andelkovic, Janet Yoon, Edwin Choy, Jeremy Howard Lewin, Javier Martin Broto, Ravin Ratan, Nam Bui, Winette T.A. Van Der Graaf, Lara E. Davis, Atrayee Basu Mallick, Hyo Song Kim, Eric Song, Jonathan Yovell, Robin Lewis Jones, Gerald J. Fetterly; Memorial Sloan Kettering Cancer Center, New York, NY; Mannheim University Medical Center, University of Heidelberg, Mannheim, Germany; University of Michigan, Michigan Medicine, Ann Arbor, MI; University of California, Los Angeles, Santa Monica, CA; Washington University School of Medicine, St. Louis, MO; Princess Alexandra Hospital, Brisbane, Australia; City of Hope, Duarte, CA; Massachusetts General Hospital, Boston, MA; Peter MacCallum Cancer Centre, Melbourne, Australia; Fundacion Jimenez Diaz University Hospital, Institute of Biomedicine of Seville, University of Seville, Seville, Spain; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Division of Oncology, Department of Medicine, Stanford University, Stanford, CA; Netherlands Cancer Institute, Amsterdam, Netherlands; Knight Cancer Institute, Oregon Health & Science University, Portland, OR; Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Immunome, Bothell, WA; The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom

Background: T2-weighted signal intensity (T2W) and tumor volume (TV) on MRI may be more sensitive than RECIST for assessing treatment effect in desmoid tumors (DT). On T2W images, hyperintense areas are associated with active fibroblast proliferation and hypointense areas are associated with loss of tumor cells and more collagenous tissue. The RINGSIDE Phase 2 study (NCT04871282) demonstrated arly and continued MRI changes in DTs with varegacestat (AL102) therapy. We report exploratory analyses of T2W, TV, and exposure-response (E-R). **Methods:** Eligible adults had histologically confirmed DT that had progressed ≥10% unidimensional growth in ≤18 months or DT-related pain requiring non-opioid medication. Participants (pts) were randomized to 3 oral varegacestat doses: 1.2 mg once daily (n = 14), 2 mg intermittent (n = 14) or 4 mg intermittent (n = 14) (intermittent = 2 days on, 5 days off). In the open-label extension (OLE), active pts received 1.2 mg once daily. We performed descriptive analysis of T2W, TV and RECIST sum of diameters (SOD), all of which were evaluated at screening, Week 16 and every 12 weeks thereafter. Linear correlations of best % changes from baseline on these assessments were evaluated with Pearson correlation coefficient. E-R modeling evaluated the time course of drug effect on TV to support selection of 1.2 mg once daily for further study. **Results:** As of April 10, 2024, median time on treatment was 23.1 months (range 0.7 – 26.6) and 23 of 42 (55%) enrolled pts were still on treatment. Line graphs of changes from baseline showed rapid and substantial reductions in T2W and TV. By Week 16, the median % changes in T2W, TV and SOD were -39%, -24%, and -8%, respectively. Median best % changes for T2W, TV and SOD were -90%, -84%, and -40%, respectively. Correlations were observed for best % changes in T2W vs SOD (R = 0.69), TV vs SOD (R = 0.82), and T2W vs TV (R = 0.89). In the 23 pts with PR/CR, median best % change was -96% (n = 21 evaluable) for T2W and -90% (n = 22 evaluable) for TV. In pts with SD, changes in T2W (n = 11 evaluable) ranged from +32% to -94%, with a median of -75%, and TV (n = 12 evaluable) ranged from +71% to -86%, with a median of +7%. Preliminary E-R analysis predicted median time to 30% decrease in TV of 3 months with the 1.2 mg once daily regimen. **Conclusions:** Substantial early and rapid reductions in T2W and TV on MRI preceded eventual RECIST responses in adults with DT treated with varegacestat. These data add to a growing body of work showing T2W and TV may play a role in evaluating treatment response in DT. Future research should evaluate the prognostic or predictive value of these imaging techniques in DT and standardization to allow for use in clinical management of DT patients. Clinical trial information: NCT04871282. Research Sponsor: Immunome.

11558 Poster Session

Long-term clinical outcome assessments in patients with tenosynovial giant cell tumor treated with vimseltinib: 1-year results from the MOTION phase 3 trial.

Vivek A. Bhadri, Hans Gelderblom, Silvia Stacchiotti, Sebastian Bauer, Andrew J. Wagner, Michiel van de Sande, Nicholas M. Bernthal, Antonio López Pousa, Albiruni Ryan Abdul Razak, Antoine Italiano, Mahbubl Ahmed, Axel Le Cesne, Christopher Tait, Amanda Vaughn Saunders, Nicholas Zeringo, Brooke Harrow, Maitreyi G. Sharma, Matthew L. Sherman, Jean-Yves Blay, William D. Tap, on behalf of the MOTION Investigators; Chris O'Brien Lifehouse, Camperdown, NSW, Australia; Leiden University Medical Center, Leiden, Netherlands; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Department of Medical Oncology, Sarcoma Center/West German Cancer Center, University Hospital Essen, University Duisburg-Essen and German Cancer Consortium (DKTK), Partner Site University Hospital Essen, Essen, Germany; Dana-Farber Cancer Institute, Boston, MA; University of California Los Angeles, Los Angeles, CA; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Princess Margaret Cancer Center, Toronto, ON, Canada; Institut Bergonié, Bordeaux, France; University College London Hospitals NHS Foundation Trust, London, United Kingdom; Gustave Roussy, Villejuif, France; Deciphera Pharmaceuticals, LLC, Waltham, MA; Centre Léon Bérard, Lyon, France; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm caused by dysregulation of the colony-stimulating factor 1 (*CSF1*) gene leading to overproduction of CSF1. Patients with TGCT often report substantial pain and stiffness, impaired physical function, and limited range of motion (ROM), supporting the need for an effective, well-tolerated CSF1 receptor (CSF1R)-targeted therapy that provides long-term improvements in functional health and quality of life (QoL). Vimseltinib is an oral, switch-control inhibitor of CSF1R. In part 1 of the MOTION phase 3 trial, vimseltinib showed statistically significant and clinically meaningful improvements vs placebo in tumor response as well as clinical outcome assessments (COAs; active ROM and patient-reported outcomes [PROs]) in patients with TGCT not amenable to surgery at week 25 (Gelderblom H, et al. *Lancet*. 2024). Here we report 1-year COA results from MOTION. **Methods:** MOTION is a global, phase 3 trial composed of double-blind (part 1; to week 25), open-label (part 2; week 25–49), and extension periods (NCT05059262). Patients received vimseltinib 30 mg twice weekly. COAs reported here include change from baseline in active ROM of the affected joint, physical function (PRO Measurement Information System physical function score [PROMIS-PF]), stiffness (worst stiffness numeric rating scale [NRS]), health status (EuroQol Visual Analog Scale [EQ-VAS]), and pain (brief pain inventory [BPI] worst pain). BPI worst pain response rate is also reported with response defined as ≥30% decrease in worst pain without ≥30% increase in narcotic analgesic use. Results are reported in patients randomized to vimseltinib during part 1 whose 1-year (week-49) assessments were complete at data cutoff (Feb 22, 2024). **Results:** Of 83 patients randomized to vimseltinib in part 1, 73 continued treatment in the open-label part of the study. Consistent with results from part 1, COAs at 1 year continued to show improvement from baseline. Mean (standard error [SE]) change from baseline in active ROM was 14.9 (5.0) percentage points. Mean (SE) changes from baseline in PROMIS-PF, worst stiffness NRS, and EQ-VAS were 6.5 (1.2), −2.7 (0.4), and 11.0 (3.5) points, respectively. Mean (SE) change from baseline in BPI worst pain was −2.8 (0.4) points, and the BPI worst pain response rate was 40% (33/83; 95% confidence interval, 29 to 51). **Conclusions:** These 1-year COA results from the MOTION phase 3 trial demonstrate durable and continued improvements in active ROM, physical function, stiffness, health status, and pain with ongoing vimseltinib treatment. Continued treatment with vimseltinib provides clinically meaningful benefit in functional health and QoL beyond week 25 for patients with symptomatic TGCT whose disease is not amenable to surgery. Clinical trial information: NCT05059262. Research Sponsor: Deciphera Pharmaceuticals, LLC.

11559 Poster Session

Daily low-dose oral temozolomide as maintenance therapy following doxorubicin plus dacarbazine in advanced leiomyosarcoma patients: An observational study.

Zhichao Tan, Jiayong Liu, Zhengfu Fan, Mengmeng Liu, Tian Gao, Shu Li; Department of Bone and Soft Tissue Tumor, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Department of Bone and Soft Tissue Tumor, Peking University Cancer Hospital, Beijing, China; Peking University Cancer Hospital & Institute, Beijing, China; Peking University Cancer Hospital, Beijing, China

Background: Doxorubicin (Dox) combined with dacarbazine (DTIC) is a standard first-line regimen for advanced leiomyosarcoma (LMS), but its long-term use is restricted due to potential cardiac toxicity. Although the addition of trabectedin to Dox, followed by trabectedin maintenance, has demonstrated improved overall survival (OS) and progression-free survival (PFS), trabectedin's limited availability in China poses a significant challenge. Given that both temozolomide (Tem) and DTIC convert to the same active metabolite (MTIC) in the body, we investigated the efficacy of daily low-dose Tem as maintenance therapy following Dox plus DTIC. Here, we present the results of this observational study. **Methods:** Eligible patients with metastatic or unresectable LMS received up to six cycles of Dox (60-70 mg/m^2, day 1) or pegylated liposomal Dox (PLD, 35–45 mg/m^2, day 1) combined with DTIC (0.9–1.2 g/m^2, day 1) every three weeks. Patients without progression after six cycles of Dox/PLD plus DTIC were transitioned to maintenance therapy with daily oral temozolomide (75 mg/m^2). Maintenance Tem was continued until disease progression. The primary endpoint was PFS during maintenance, assessed by investigators. Secondary endpoints included OS and safety. PFS and OS were defined as the time from initiation of oral Tem until disease progression and death, respectively. **Results:** Between May 2022 and December 2024, 20 patients were enrolled, with a median age of 55 years. All patients were female. The primary tumor site was uterine in 45% of cases and non-uterine in 55%; 90% had metastatic disease, and 10% had locally advanced disease. Seventeen patients were evaluable for efficacy. The median PFS during maintenance was 7.1 months, with three patients achieving disease control for over 12 months. Treatment was generally well-tolerated, with the most common adverse events (AEs) being grade I/II nausea (80%), vomiting (45%), and white blood cell reduction (25%). Serious AEs leading to treatment discontinuation occurred in two patients: one due to severe vomiting and one due to elevated liver enzymes. **Conclusions:** Daily low-dose oral temozolomide appears to be an effective and well-tolerated maintenance therapy following Dox plus DTIC for patients with advanced LMS. This approach may offer a viable alternative for patients in regions where trabectedin is unavailable. Research Sponsor: None.

11560 Poster Session

A phase II, multicenter trial of the combination of chidamide and toripalimab in patients with advanced soft tissue sarcoma: Efficacy updates.

Xing Zhang, Ruiqing Peng, Peng Zhang, Wenhua Zhan, Qiuzhong Pan, Bushu Xu, Dongchun Hong, Yi Que; Melanoma and Sarcoma Medical Oncology Unit, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; Melanoma and Sarcoma Medical Oncology Unit, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-Sen University, Guangzhou, China; Department of Bone and Soft Tissue, the Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; Department of Radiation Oncology, General Hospital of Ningxia Medical University, Yinchuan, NA, China; Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: Chidamide is an oral subtype-selective histone deacetylase (HDAC) inhibitor which is effective on the patients with hematological tumors and could be hoped to enhance the efficacy of checkpoint blockade therapies and regulate the host immune response. Here, we report the updates of preliminary results of the combination of Chidamide and Toripalimab in soft tissue sarcoma (STS) patients. **Methods:** An open-label, single arm, multicenter, phase II study of Chidamide with Toripalimab in patients with advanced STS was conducted. Patients who were with failure or intolerance of standard systemic therpy, or no existed standard treatment, are eligible. Patients who had underwent HDAC inhibitors and immune checkpoint inhibitors treatment were excluded. All patients received Chidamide orally at 30mg twice weekly in combination with intravenous Toripalimab 240mg every 21 days until progression or unaccepte toxicity. The primary endpoint was RECIST1.1 objective response rate (ORR). The secondary endpoint included progression free survival (PFS), overall survival (OS), disease control rate (DCR) and safety. **Results:** At the data cut-off date (January, 2025),sixty-nine patients with advanced STS were enrolled. The median age of the patients was 47 years (range, 16 to 68) and the median prior lines of therapy were 2 (range, 0 to 5). The main subtypes included leiomyosarcoma (29%), well/dedifferentiated liposarcoma (36.2%), undifferentiated sarcoma(7.2%), myxoid/round cell liposarcoma (4.3%), and osteosarcoma (4.3%). Treatment was well tolerated with the most common adverse events mainly in grade 1-2, including anemia(55.1%), hypothyroidism(44.9%), leukopenia(33.3%), thrombocytopenia (30.4%), neutropenia(24.6%), nausea/vomit(24.6%), and fatigue (15.9%). Of the grade 3–4 adverse events, the most common were neutropenia(27.5%), thrombocytopenia (23.2%), leukopenia(14.5%), nausea/vomit(10.1%) and anemia(1.4%). Among 69 efficacy-evaluable patients, the ORR and DCR were 29% and 73.9%, respectively. The median time to an initial response was 5 months (95%CI 3-7), and the median PFS was 7.1 months (95%CI 4.0-10.2) , and the median OS was not reached. **Conclusions:** Chidamide with Toripalimab every 21 days was well tolerated and showed promising efficacy in patients with advanced STS. The exploratory biomarker study is ongoing. Clinical trial information: NCT04025931. Research Sponsor: None.

11561 Poster Session

Detecting hotspots of intra- and transchromosomal fusions in liposarcomas by RNA sequencing.

Dmitrii Grachev, Danil Ivanov, Oleg Baranov, Vladimir Kushnarev, Melissa Clemons, Sheila Yong, Nikita Kotlov, Konstantin Chernyshov, Alexander Bagaev, Nathan Hale Fowler, Anthony Paul Conley, Gregory Michael Cote, Sant P. Chawla; BostonGene, Corp., Waltham, MA; BostonGene Corporation, Waltham, MA; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Center for Sarcoma and Connective Tissue Oncology, Department of Hematology and Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Sarcoma Oncology Center, Santa Monica, CA

Background: Liposarcoma (LPS) is characterized by unstable genomes and high occurrence of gene fusions. Hotspots of both recurrent and non-recurrent gene fusions can provide information about structural alterations in certain LPS subtypes. For instance, myxoid (M) LPS expresses the oncogenic *FUS-DDIT3* protein and is known to be fusion-driven. Moreover, disrupted locus 12q13-15 is an important feature of well-dedifferentiated (WD) and dedifferentiated (DD) LPS, and is the site of copy number alterations (CNAs) and gene fusions. Here, we used RNA sequencing to uncover hotspots of intra- and transchromosomal gene fusions in LPS patient samples, identifying potentially clinically relevant events in certain chromosomal regions. **Methods:** The BostonGene internal LPS cohort (n=150) was analyzed by bulk whole-transcriptome sequencing, using STAR-fusion for sequence calling. Quality control was performed using FastQC, FastQ Screen, RSeQC, and MultiQC. Tumor purity was assessed via pathological and bioinformatics examination with a threshold of 20%. One sample Poisson rate test was used to evaluate statistical significance of gene fusion hotspots. **Results:** We identified 4,080 gene fusions among four LPS subtypes (DDLPS, WDLPS, MLPS, and PLPS - pleomorphic LPS). Of those, 2,302 (56.4%) were intrachromosomal and 1,778 (43.6%) were transchromosomal. Over half of these fusions (1,263/2,302 intrachromosomal fusions, 54.9%; 1,047/1,778 transchromosomal fusions, 58,9%) were detected on chromosome 12. Most identified fusions occurred in the 12q13-15 region (q-value < 0.001), with q15 being especially prevalent in transchromosomal fusions (q-value < 0.001). The most prevalent recurrent fusion across our LPS cohort was *FUS-DDIT3* (N=21, MLPS samples). Another notable recurrent fusion was *TRIO-TERT* (N=4, DDLPS). We also identified extended gene fusion hotspots in regions containing important oncogenes such as *MDM2* and *FRS2* in LPS subtypes (DDLPS, WDLPS, PLPS) that are not considered fusion-driven (Table). These findings suggest an oncogenic role of such fusions in these LPS subtypes, along with known CNAs like *MDM2* amplification. **Conclusions:** Our comprehensive transcriptomic analysis of gene fusions in LPS samples uncovered both new and established hotspots of chromosomal rearrangements. Identification of such hotspots improves our understanding of LPS oncogenesis and thus can enhance the diagnostic accuracy and discovery of new biomarkers. Research Sponsor: None.

Hotspots of gene fusions in liposarcoma.

Hotspot cytoband	Diagnosis	q-value	Important genes
1q23.3	DDLPS	< 0.001	*ATF6*
1q24.3	DDLPS, WDLPS	< 0.001	*DNM3*
12q13.3	MLPS	< 0.001	*DDIT3*
12q14.1	DDLPS, WDLPS	< 0.001	*CDK4*
12q14.3	DDLPS, WDLPS	< 0.001	*HMGA2, YEATS4*
12q15	DDLPS, WDLPS, PLPS	< 0.001	*MDM2, FRS2, CPM*
16p11.2	MLPS	< 0.001	*FUS*

11562 Poster Session

Treatment discontinuation in desmoid tumors: Factors associated with better outcomes after sorafenib discontinuation.

Irvin Yi, Pedro Henrique Benfatti Gomes, Nicole Janell Hardy, Brandon Edward Rose, Chang Yu-Cherng, Steven Bialick, Emily E. Jonczak, Gina Z. D'Amato, Hari Anant Deshpande, Roberto Carmagnani Pestana, Bruna Bianca Lopes David, Jonathan C. Trent, Fernando Augusto Batista Campos, Philippos Apolinario Costa; Yale School of Medicine, New Haven, CT; A.C. Camargo Cancer Center, São Paulo, Brazil; University of Connecticut Health Center, Farmington, CT; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Yale Cancer Center, New Haven, CT; Hospital Israelita Albert Einstein, São Paulo, Brazil; Brazilian National Cancer Institute, Rio De Janeiro, Brazil

Background: Sorafenib has shown effectiveness in managing desmoid tumors. However, the optimal duration of systemic therapy and the outcomes following its discontinuation remain unknown. This study investigates the outcomes of patients who discontinued sorafenib, aiming to provide guidance for clinicians on treatment cessation. **Methods:** We conducted an international, multi-institutional retrospective analysis of patients treated with sorafenib who discontinued therapy with no immediate plans to initiate a new treatment. We assessed whether the duration of sorafenib use (6 months, 1 year, or 2 years), the reason for discontinuation (side effects or shared decision-making), and the treatment response at the time of discontinuation influenced the likelihood of requiring subsequent treatment (treatment free survival, TFS) or experiencing disease progression (progression free survival, PFS). Kaplan-Meier curves were used for survival analysis, and group comparisons were performed using the log-rank test. **Results:** Between 2005 to 2022, a total of 48 patients were identified meeting the eligibility criteria. Three (6%) patients received therapy for less than 6 months, thirteen (27%) received less than 12 months, and thirty (63%) received less than 24 months. Seventeen (35%) patients stopped therapy due to side effects with the remaining thirty-one (65%) patients discontinuing due to other reasons, such as patient preference, provider decision, or payment coverage. Four (8%) patients experienced progression of disease while 38 (79%) had stable disease or partial response. The most common side effects were diarrhea (52%), palmar-plantar erythrodysesthesia syndrome (46%), and fatigue (23%). Patients who received less than 6 months of sorafenib treatment prior to discontinuation had a TFS of 10.1 months, compared to 54.5 months for over 6 months of duration ($p < 0.001$). At the 12-month mark, less than 12 months had median TFS of 49.1, compared to 54.5 for longer ($p = 0.2$). At the 24-month mark, less than had a median TFS of 49.1, compared to 54.5 for longer ($p = 0.1$). Other factors did not emerge as statistically significant ($p > 0.05$). **Conclusions:** Our data demonstrates the duration of sorafenib treatment is a significant indicator for future treatment need. Reaching the 6-month mark could be indicative of an important checkpoint, although the 1- and 2-year marks are also associated with a clinically, but not statistically, significant reduction in likelihood for future treatment. Clinicians and patients should be aware that duration is an important consideration for future outcomes in desmoid tumor treatment, and to factor it into shared decision-making. Research Sponsor: None.

11563 Poster Session

Safety and antitumor activity of ^{177}Lu-catelase: A preliminary clinical study in soft tissue sarcoma.

Jiayong Liu, Zhichao Tan, Xiaoyi Guo, Jiayue Liu, Jinxing Nian, Meng Yuan, Hua Zhu, Zhi Yang; Department of Bone and Soft Tissue Tumor, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; NMPA Key Laboratory for Research and Evaluation of Radiopharmaceuticals, Department of Nuclear Medicine, Peking University Cancer Hospital & Institute, Beijing, China; Jiaxing Fabo Xintian Pharmaceutical Technology Co., Ltd, Beijing, China; Department of Nuclear Medicine, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, Beijing, China

Background: Localized radiotherapy with radioisotope injections holds promise but is limited by poor tumor retention and hypoxia. To overcome these challenges, we developed ^{177}Lu-CAT/ALG, a hydrogel formulation containing catalase labeled with ^{177}Lu and sodium alginate (ALG). Upon injection, endogenous calcium rapidly forms a hydrogel, securing ^{177}Lu-CAT within the tumor, alleviating hypoxia, and enhancing therapeutic efficacy. Preclinical studies demonstrated sustained hypoxia relief, superior tumor retention, and significant antitumor activity. This phase 1 trial evaluates the safety and preliminary efficacy of ^{177}Lu-CAT/ALG in patients with soft tissue sarcoma (STS). **Methods:** Patients with locally advanced STS underwent baseline metabolic and volumetric assessments using ^{18}F-FDG PET/MR imaging. Intratumoral doses were calculated using the OLINDA 2.0 Sphere Model, with ultrasound-guided injections administered every 8 weeks. SPECT imaging assessed tumor retention at 2, 24, 96, and 168 hours post-injection. Efficacy was evaluated bi-monthly per PERCIST criteria. Primary endpoints included tumor retention and safety (CTCAE v5.0). Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** Seven patients with locally advanced STS were treated, with a median tumor size of 8.5 cm. SPECT imaging confirmed that at least 60% of ^{177}Lu-CAT/ALG remained within tumors at 168 hours. The most common adverse events (AEs) were grade 1-2 reductions in white blood cell count (4/7 patients). One patient experienced a grade 4 AE (thrombocytopenia). Stable disease was observed in two patients, with disease control lasting 16.53 and 12.8 months. As of the data cutoff, one patient remains on treatment. Pathological analysis of a tumor specimen from a patient with increased tumor volume on PET/MR revealed 70% necrosis after resection. **Conclusions:** ^{177}Lu-CAT/ALG demonstrated a favorable safety profile, sustained tumor retention, and encouraging antitumor activity in patients with locally advanced STS. These results highlight the potential of ^{177}Lu-CAT/ALG as a novel therapeutic approach and support further evaluation in larger trials. Clinical trial information: NCT05985278. Research Sponsor: None.

Characteristics of participants.

No.	Gender	Age	Tumor type	Primary tumor location	Tumor size	Number of injections	Mean dose of injections (range)/ mCi	Outcomes
1	F	41	LGSTS, NOS	right scapular region	8.6	5	23.30(16.8-29.1)	On treatment
2	F	55	FS	Right chest wall	9.3	1	14.3	PD
3	F	58	LGSTS, NOS	Left chest wall	4.7	4	9.6 (7.0-10.7)	PD
4	F	51	LMS	Abdominal wall	7.3	1	31.9	PD
5	F	47	EMFS	Right chest wall	9.6	1	32.4	PD
6	M	60	UPS	Neck	7.6	1	23.8	PD
7	M	67	MFS	Right elbow	8.5	1	15.7	PD

LGSTS: low grade soft tissue sarcoma, NOS: not otherwise specified, FS: fibrosarcoma, LMS: leiomyosarcoma, EMFS: epithelioid myxofibrosarcoma, UPS: undifferentiated pleomorphic sarcoma, MFS: myxofibrosarcoma, PD: progressive disease.

11564 Poster Session

Doxorubicin-based chemotherapy vs gemcitabine/docetaxel in uterine leiomyosarcoma (ULMS).

Stephanie Soewito, Heather Y. Lin, Marianne Zoghbi, Cong Pan, Peter Young, Dejka M. Araujo, Anthony Paul Conley, J. Andrew Livingston, Joseph Aloysius Ludwig, Michael Nakazawa, Ravin Ratan, Vinod Ravi, Neeta Somaiah, Maria Alejandra Zarzour, Shreyaskumar Patel, Larissa Alejandra Meyer, Pamela T. Soliman, Heather Lyu, Elise F. Nassif Haddad, Ryan A. Denu; University of Texas Health Science Center at Houston, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ULMS is an aggressive uterine smooth muscle cancer. Surgery is standard for localized/advanced ULMS, and the use of adjuvant chemotherapy is controversial. Treatment may involve combination cytotoxic chemotherapy, typically doxorubicin-based regimens (D) or gemcitabine plus docetaxel (GT), which have poor (20-30%) response rates and high toxicity. Given the lack of randomized trial data, this single-center retrospective study compared D vs GT in the adjuvant and metastatic settings of ULMS. **Methods:** We included patients with confirmed histologic diagnosis of uterine leiomyosarcoma between 2000 and 2024 treated at MD Anderson Cancer Center with either D or GT. Patients were stratified by localized disease and receipt of adjuvant chemotherapy or metastatic disease and receipt of palliative chemotherapy with D or GT in the first-line setting. The primary objective was to assess recurrence-free survival (RFS) in those with localized tumors and progression-free survival (PFS) in those with metastatic tumors treated with either D or GT. RFS and PFS were defined as the time interval from the start time of first line chemotherapy (D or GT) to the time of recurrence/progression or death, whichever occurred first. Kaplan Meier and log rank tests were used to assess survival outcomes. Cox proportional hazards (PH) modeling evaluated whether either regimen independently predicted survival with adjustment for age, primary tumor size, and mitotic index. Data collection is ongoing, and propensity score matching will be performed. **Results:** We included 76 patients, including 36 with primary localized ULMS and 40 with advanced ULMS. In patients with localized disease, there was no significant difference in RFS between those treated with D vs GT in univariate (p = 0.17) or multivariate (HR (95% CI) = 1.21 (0.35, 4.15), p = 0.76) analyses. In patients with metastatic disease, GT was associated with inferior PFS than those treated with D (HR (95% CI) = 4.45 (1.38, 14.29), p = 0.01) after adjusting for age and primary tumor size in the multivariate Cox PH model. **Conclusions:** Treatment with D was associated with improved PFS for metastatic ULMS compared to treatment with GT. No significant difference in RFS was observed between the two regimens for localized disease. However, the study may have limited power to detect differences due to small sample size. Updated data analyses with a larger cohort will be presented at the meeting. Research Sponsor: None.

	Localized ULMS (n = 36)	Metastatic ULMS (n = 40)
Age of diagnosis (median, years)	51.0	52.3
Primary tumor size (median, cm)	10.1	11.0
Mitotic Index (>10 per 10 HPF)	77.8% (n = 28)	82.5% (n = 33)
	D GT	D GT
	16.7% (n = 6) 83.3% (n = 30)	30% (n = 12) 70% (n = 28)
RFS/PFS (median, months)	10.8 (7.8, 23.0)	7.2 (4.5, 9.2)
HR (95% CI)	1.21 (0.35, 4.15)	4.45 (1.38, 14.29)
p-value	0.7612	0.0122
Overall Survival (median, years)	6.6 (2.5, 10.3)	4.6 (3.7, 6.7)

11565 Poster Session

Heterogeneity in epithelioid hemangioendothelioma (EHE): Insights into common and organ-specific tumor pathways.

Tom Wei-Wu Chen, Chia-Lang Hsu, Wen-Hsuan Yu, Jen-chieh Lee, Hsuan-Ying Huang; National Taiwan University Hospital, Taipei, Taiwan; National Taiwan University Hospital, Taipei City, Taiwan; Kaohsiung Chang Kung Memorial Hospital, Kaohsiung, Taiwan

Background: EHEs are ultra-rare sarcomas that can arise from various organs, with the primary site being an important prognostic factor. We hypothesized that EHEs from different organs harbor heterogeneous tumor cells. Understanding key pathways associated with this heterogeneity may lead to improved therapies for EHE patients. **Methods:** EHE samples from different primary sites with confirmed pathognomonic gene rearrangements were analyzed. Spatial transcriptomics was performed on FFPE samples using the Visium CytAssist platform. Pathway analyses were conducted with AUCell, and cell compositions were estimated using XCell. A second platform, Xenium, was used for confirmation. **Results:** Eight EHE patients with different primary organ sites (liver 3, lung & pleura 2, bone 2, soft tissue 1) and gene rearrangements (CAMAT1 FISH+ 6, TFE3 FISH+ 1, WWTR1 FISH+ 1) had spatial transcriptomic results. Unsupervised clustering identified 35 different clusters and EHE clusters were defined in accordance to histology and vascular markers (CD31, CD34, and ERG). These clusters could be broadly categorized into "common (non-organ-specific)" clusters, observed in three or more organ types, and "organ-specific" clusters. Common clusters showed higher levels of stem-like endothelial cell markers and increased TGF-beta and mTORC1 pathway activity, which may explain the clinical benefit of sirolimus in EHE. Using liver EHEs as an example, the liver-specific cluster demonstrated a fibroblast/mesenchymal stromal cell differentiation pattern not observed in EHEs from other organs. GDF-15, which is associated with aggressiveness in EHE and cachexia, was significantly higher expressed in common than organ-specific cluster. In liver and bone EHEs, clusters with high GDF-15 expression tend to have higher TGF-beta signaling and lower dendritic cells, implying the role of GDF-15 in EHE with immune regulation. These findings were validated in Xenium analysis. **Conclusions:** This study shows that EHE tumors share certain core pathways but also exhibit organ-specific differentiation patterns, which may underlie their variable prognoses. The coexistence of both "common" and "organ-specific" clusters highlights the importance of personalized treatment strategies and paves the way for more targeted therapeutic development in EHE. Research Sponsor: National Taiwan University Hospital.

11566 Poster Session

Molecular profiling and prognosis of spindle cell/sclerosing rhabdomyosarcoma: A report from the Chinese PPOG trial.

Suying Lu, Junting Huang, Feifei Sun, Juan Wang, Jia Zhu, Yi Que, Mengzhen Li, Zijun Zhen, Yizhuo Zhang; Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: Spindle cell/sclerosing rhabdomyosarcomas (SSRMS) is a rare variant of rhabdomyosarcoma, recognized as a distinct pathological entity in the most recent WHO classification. However, the molecular profile and clinical outcomes of patients with SSRMS remain poorly understood. The Pediatric Precision Oncology Group (PPOG) is a multicenter project aimed at characterizing tumor molecular profiles in pediatric oncology patients across China. **Methods:** From January 2016 to July 2024, a total of 70 patients with SSRMS were enrolled in the PPOG (NCT05076071) trial, with 57 patients meeting the criteria for clinical analysis. Targeted gene sequencing (830 DNA and 395 RNA) was conducted on tumor samples from 43 patients, while whole-transcriptome analysis was performed on tumor samples from 13 patients to assess gene expression. The Kaplan-Meier method was employed to estimate overall survival (OS) and event-free survival (EFS). **Results:** The median follow-up time was 48 months (range: 6.3–160.8 months). The 4-year EFS rates for patients with low risk (n = 16), intermediate risk (n = 27), and high risk (n = 14) were 92.9%, 79.3%, and 12.9%, respectively ($P < 0.0001$). The 4-year OS rates for these groups were 68.8%, 51.2%, and 39.7%, respectively (P = 0.2046). The 4-year EFS rates for patients aged < 10 years (n = 33) and ≥ 10 years (n = 24) were 66.7% and 31.7%, respectively (P = 0.017). The 4-year OS rates for these groups were 71.4% and 63.8%, respectively (P = 0.192). The most commonly recurrently altered genes were MYOD1 (48.8%), PIK3CA (25.6%), CDKN2A (23.3%), CDKN2B (16.3%), and IGF1R (9.3%) mutations. All 21 cases with MYOD1 mutations showed a p.L122R (c. T365G) mutation, consistent with previous reports. Gene interaction analysis shows that MYOD1 mutation frequently occur alongside CDKN2B mutation. Compared to the MYOD1 wild-type group, the MYOD1 mutant group has a significantly higher incidence of CDKN2B mutation, as well as higher rates of PIK3CA and IGF mutations, and lower rates of NOTCH1 and TP53 mutations. Eighteen fusion genes were detected in 30.2% (13/43) of SSRMS patients, with the most common being BRAF fusion (4.6%) and ROS1 fusion (4.6%). Actionable mutations were identified in 76.7% of patients, with the most frequently matched targeted therapies including PI3K inhibitors (32.3%), CDK4/6 inhibitors (21.2%), and MEK inhibitors (11.5%). Compared to the MYOD1 wild-type group, RNA differential expression analysis revealed a significant upregulation of the PI3K-AKT pathway in the MYOD1 mutant group. The infiltration levels of CD4+ T cells and macrophages in the MYOD1 mutant group were significantly higher than those in MYOD1 wild-type group. **Conclusions:** The MYOD1 mutant group and the MYOD1 wild-type group exhibit distinct molecular characteristics. Larger sample studies are needed to clarify the molecular features and risk stratification of SSRMS. Clinical trial information: NCT05076071. Research Sponsor: None.

11567 Poster Session

Impact of time to relapse (TTR) and metastasectomy (MTS) on survival in leiomyosarcoma (LMS): A CanSaRCC study.

Haydée Williams Sanchez, Erica C. Koch Hein, Hagit Peretz Soroka, Geoffrey Alan Watson, Carolyn Nessim, Caroline Holloway, Tristan Wild, Brookelyn Biffart, Abha A. Gupta, Albiruni Ryan Abdul Razak, Abdulazeez Salawu; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Center, University Health Network, University of Toronto, Toronto, ON, Canada; Division of Medical Oncology, Mount Sinai Hospital, Sinai Health, University of Toronto, Toronto, ON, Canada; University of Ottawa - Ottawa General Hospital, Ottawa, ON, Canada; Division of Radiation Oncology, BC Cancer, Victoria, BC, Canada; Department of Surgery, The Ottawa Hospital and Research Institute, Ottawa, ON, Canada; Division of Radiation Oncology, BC Cancer, University of British Columbia, Victoria, BC, Canada

Background: Approximately 40% of LMS patients (pts) experience relapse despite standard care of surgical resection ± radiotherapy. Upon relapse, pts with advanced disease receive palliative systemic therapy. Often reserved for pts with oligometastatic disease, the role of MTS remains unclear due to a lack of randomized trials. Longer time from curative surgery to relapse (TTR) is associated with better outcomes in LMS pts who undergo MTS but its prognostic value has not been established in those treated without MTS. This study evaluates the effect of TTR on outcomes in LMS pts with metachronous metastases treated with systemic therapy ± surgery. **Methods:** This real-world study included advanced LMS pts treated at 4 Canadian sarcoma centers (2010–2022) who underwent curative resection, subsequent relapse, and systemic treatment ± MTS. Data were retrieved from the ethics-approved Canadian Sarcoma Research and Clinical Collaboration (CanSaRCC) database. Primary and secondary endpoints were overall survival (OS) stratified by TTR (< 6 vs ≥6 months from the completion of curative resection); and MTS, respectively. Exploratory analysis evaluated the impact of MTS in pts with low disease burden at relapse (< 2 sites). Kaplan-Meier survival analysis and log-rank tests were used to compare OS, and Cox proportional hazards models identified independent predictors, with $p < 0.05$ considered significant. **Results:** A total of 113 pts (median age 56y) were included. Median follow-up was 38.4 months (mo). Majority (n = 93, 82%) were female and 38 (34%) had uterine leiomyosarcoma (uLMS). Relapse occurred in 109 pts (96%) with 73/109 pts (70%) having < 2 metastatic sites at relapse. TTR was < 6 months (TTR < 6) in 31/109 pts (28%) and 43/109 pts (39%) underwent MTS. Pts with TTR ≥6 months (TTR≥6) had significantly longer median OS (mOS) than those with TTR < 6 (32.9 vs 15.6mo, p = 0.006). Metastasectomy was associated with a significantly longer mOS in the whole cohort (50.4 vs 17.6mo, $p < 0.0001$) as well as the subgroup of patients with < 2 metastatic sites at relapse (50.6 vs 15.6mo, $p < 0.0001$). The mOS was 50.4 vs 24.7mo in pts with TTR≥6 who underwent MTS and those who did not, respectively ($p < 0.0001$). Among pts with TTR < 6 who had MTS, median OS was 44.8mo compared with 9.4mo in pts without surgery (p = 0.005). No other variables (e.g., tumor grade, primary site, metastatic burden, gender, or age) impacted OS. Both MTS (HR 0.26, 95% CI 0.16–0.49, p = 0.000) and TTR ≥ 6 (HR 0.55, 95% CI 0.33–0.91, p = 0.02) remained independent predictors of favorable OS in multivariate analysis. **Conclusions:** TTR≥6 was associated with longer OS in LMS pts. OS improved significantly with MTS, particularly in pts with longer TTR, though those with TTR < 6 also benefited to a lesser extent. These results underscore the role of MTS as part of an individualized treatment strategy to optimize outcomes in advanced LMS. Research Sponsor: None.

11568 Poster Session

A phase Ib/II trial of radiotherapy combined with doxorubicin and PD-1 antibody for localized high-risk limbs and trunk soft tissue sarcomas.

Yan Wang, Shujuan Zhou, Lanyue Xu, Yue Su, Yaqi Wang, Ruiyan WU, Lijun Shen, Juefeng Wan, Yu Xu, Yong Chen, Wangjun Yan, Zhen Zhang; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Sichuan Clinical Research Center For Cancer, Sichuan Cancer Hospital & Institute, 510100, China; Fudan University Shanghai Cancer Center, Shanghai, China; Fudan University Shanghai Cancer Center; Shanghai Medical College, Fudan University, Shanghai, China; Department of Musculoskeletal Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Background: Localized high-risk soft tissue sarcomas (STSs) presents a therapeutic challenge due to limited preoperative treatment options. Radiotherapy (RT) and Doxorubicin (DOXO) are well-established immunogenic cell death inducers [1-3], which are capable of boosting the effects of immunotherapy even in "cold" tumors. This study aims to evaluate the safety and efficacy of a preoperative triple combination of RT, DOXO, and the PD-1 antibody for STS. **Methods:** In this Phase Ib/II trial (NCT05774275), up to 52 patients with localized high-risk STSs will be enrolled. Participants will receive RT (BED = 50-60 Gy), combined with DOXO and PD-1 antibody (Sintilimab, SIN 200 mg, Day 1) every three weeks for four cycles prior to surgery. In Phase Ib (3+3 design), patients will receive Pegylated liposomal doxorubicin (PLD, 37.5 mg/m^2 or 30 mg/m^2, i.v., Day 1) to establish the recommended Phase 2 dose (RP2D). In Phase II, DOXO will be administered as PLD at RP2D or as Doxorubicin Hydrochloride (Adriamycin, ADM, 75 mg/m^2 i.v., Day 1). The primary endpoint is the objective response rate (ORR), while secondary endpoints include the rate of pathological complete response (pCR) and near pCR (defined as $<$ 10% viable tumor cells), survival and safety. **Results:** From September 2022 to January 2025, 33 patients (26 in limbs and 7 in trunks) were enrolled. The median age was 50 years (range 19-75), with 17 males, and 13 patients had prior surgeries. 29 tumors were histological grade 3. No dose-limiting toxicities (DLT) were observed in the first six patients receiving PLD (37.5 mg/m^2, i.v., Day 1, q3w), confirming the RP2D. Among the 28 radiological evaluable patients, 2 achieved complete response (CR), 12 achieved partial response (PR), and 11 had stable disease, resulting in an ORR of 50.0% and a disease control rate (DCR) of 89.2%. In addition, among 24 pathological assessable patients, 14 (58.3%) achieved pCR or near-pCR. Two patients (9.5%) experienced major wound complications. They underwent secondary operation and readmission to hospital for wound care, respectively. Other serious adverse events (SAE) include Grade 3 dermatitis (17.9%) and Grade 3-4 neutropenia (7.1%). No G5 SAE were reported. Median progression-free survival and overall survival have not yet been reached. **Conclusions:** The combination of RT, DOXO, and SIN showed potential efficacy and tolerable toxicity in high-risk localized limbs and trunk STS. The trial is still ongoing. Clinical trial information: NCT05774275. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation; Y-Young2020-0477; National Natural Science Foundation of China; 82373132.

11569 Poster Session

Self-assembled patient-derived tumor-like cell clusters for personalized drug testing in diverse sarcomas.

Tian Gao, Xinyu He, Junyi Wang, Jiayong Liu, Xiongbing Hu, Chujie Bai, Shenyin Yin, Yunfei Shi, Yanming Wang, Zhichao Tan, Fang Cao, Shu Li, Yanjie Shi, Ruifeng Xue, Juan Li, Yang He, Zhiwei Fang, Zhengfu Fan, Jianzhong Xi; Department of Bone and Soft Tissue Tumor, Peking University Cancer Hospital, Beijing, China; State Key Laboratory of Natural and Biomimetic Drugs, Department of Biomedical Engineering, College of Future Technology, Peking University, Beijing, China; Department of Bone and Soft Tissue Tumor, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Department of Bone and Soft Tissue Tumor, Peking University Cancer Hospital & Institute, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University Cancer Hospital & Institute, Beijing, China; Peking University Cancer Hospital, Beijing, China; College of Future Technology, Peking University, Beijing, China; College of Future Technology Peking University, Beijing, China

Background: Soft tissue sarcomas (STS) are rare malignancies with over 100 distinct histological subtypes. Their rarity and heterogeneity pose significant challenges to identifying effective therapies, and approved regimens show varied responses. Several patient-derived tumor models have emerged recently. However, STS present a challenge in developing preclinical drug-testing models due to their non-epithelial and complex nature. **Methods:** Here we report a model termed patient-derived tumor-like cell clusters (PTCs) derived from STS patients. PTCs result from the self-assembly and proliferation of mesenchymal stem cells (MSCs), epithelial cells, and immune cells, faithfully recapitulating the morphology and function of the original tumors. This is an trial to assess the feasibility and predictive value of a standardized PTC-based test to differentiate efficacy of the patients' clinical drug regimens. The study was conducted at Peking University Cancer Hospital and was approved by the local ethical review board. The patients and corresponding PTCs were divided into three sets: characterization and storage set, assay set and validation set. The characterization and storage set were used to characterize PTCs in comparison with original tumor samples or stored for future study. The assay set was separated into two groups to determine the drug efficacy concentration of a targeted therapy or chemotherapy due to their different action mechanisms. The validation set was used to compare the consistency between PTC drug assays and clinical outcome. We then conducted comparative analyses between PTCs and tumor spheres, as well as between PTCs and paired tumor samples. **Results:** From 2019 to the 2025, we obtained 254 samples (155 surgical, 98 puncture, and 1 ascites sample) to generate PTCs, covering tens of sarcoma classifications, with an overall success ratio of 94.9%, ranging from 85.7% to 100%. A total of 3,740 differentially expressed genes (DEGs) were identified between PTCs and tumor spheres, while 1,222 DEGs were identified between PTCs and tumor samples. Through standardized culture and drug-response assessment protocols, PTCs facilitate personalized drug testing, evaluating hundreds of therapies within two weeks. PTCs demonstrate an overall predictive accuracy of 78.3% for all clinical outcomes and 100% accuracy distinguishing CR/PR from PD, could serve as a valuable tool for personalized medicine. **Conclusions:** These findings revealed that PTCs as a tool to better understand the biology of individual tumors and characterize the landscape of drug resistance and sensitivity in sarcoma. These results underscore the potential of PTCs for prospective use in clinical decision-making therapy selection.
Research Sponsor: None.

Population-based assessment of leiomyosarcoma (LMS) and cancers in the Li-Fraumeni syndrome (LFS) spectrum: Implications for genetic testing criteria.

Wendy Kohlmann, Karen Curtin, Michael J. Madsen, Nicola J. Camp, Joanne M. Jeter, Mandy L. Ballinger, David Morgan Thomas, Judy Ellen Garber, Joshua David Schiffman; Hunstman Cancer Institute at the University of Utah, Salt Lake City, UT; Huntsman Cancer Institute, Salt Lake City, UT; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; City of Hope, Duarte, CA; Centre for Molecular Oncology, University of New South Wales, Sydney, NSW, Australia; Dana-Farber Cancer Institute, Boston, MA

Background: Data regarding the heritability of rare tumors is limited and may prevent incorporation into genetic testing criteria. This study utilized the Utah Population Database (UPDB) to evaluate cancer risks among LMS cases and their relatives and the prevalence of meeting Chompret criteria (ChC) for LFS genetic testing. **Methods:** Between 1995-2021, 429 LMS cases with UPDB genealogies were identified from the Utah Cancer Registry. Diagnoses were confirmed, when possible, by pathology reports. Cases were individually age- and sex-matched 1:5 to population controls with similar pedigrees and follow-up (n=2145 controls). Cancers from 1966-2021 were obtained for study subjects and their first- through third-degree relatives. LFS spectrum cancers included breast, soft tissue sarcomas, osteosarcomas, CNS/brain, and adrenocortical. Hazard rate ratio (HRR) estimates of self- and familial relative cancer risks in LMS compared with controls was calculated from a Cox model adjusting for the number of relatives, degree of relatedness, and person-years at risk. **Results:** A 2.2-fold risk ($p<0.001$) of a cancer in the LFS spectrum was seen in cases with a non-uterine LMS site (n=323) at any age and a 4.5-fold risk ($p<0.001$) for developing an LFS cancer at age <50 y. Non-uterine LMS cases had similarly increased risks for developing a non-LFS-spectrum cancer at any age and <50y (Table). Increased risk of LFS or non-LFS-spectrum cancer was not seen in uterine LMS cases (n=106). Although increased cancer risk was not generally observed in relatives of LMS cases compared with control relatives, we observed that non-uterine LMS and their first-degree relatives had an increased risk of colorectal cancer (CRC) (Table). CRC is not an LFS cancer but is known to occur in LFS families. Excluding the LMS diagnosis, non-uterine LMS cases were more likely to meet ChC compared with controls (Table 1). Uterine LMS cases were no more likely to meet ChC than their respective controls. **Conclusions:** LMS is associated with cancers outside the spectrum, and further studies are needed to determine if LMS is associated with other cancer predisposition genes. Family history should be evaluated broadly and not restricted to ChC. As uterine LMS appears less likely to be associated with genetic predisposition, considering non-uterine and uterine cases separately may be important for future studies of the genetic basis of LMS. Research Sponsor: National Cancer Institute; Award Number P50CA272170; National Cancer Institute; P30CA042014; National Cancer Institute's SEER Program; Contract No. HHSN261201800016I; US Centers for Disease Control and Prevention's National Program of Cancer Registries; Cooperative Agreement No. NU58DP007131; Huntsman Cancer Foundation.

Cancer risks in LMS cases and relatives compared with controls.

	Non-uterine LMS =323, Controls=1615				Uterine LMS =106, Controls=503			
	Case HRR	*P*	FDR HRR	*P*	Case HRR	*P*	FDR HRR	*P*
LFS cancer	**2.2**	**<0.001**	1.1	0.68	0.6	0.36	1.3	0.24
LFS cancer <50	**4.5**	**<0.001**	1.2	0.72	1.3	0.77	2.1	0.08
Non-LFS cancer	**2.2**	**<0.001**	1.2	0.06	1.0	0.98	1.1	0.44
Non-LFS cancer <50	**4.1**	**<0.001**	1.2	0.38	1.5	0.52	1.4	0.35
Colorectal	**2.7**	**0.04**	**1.6**	**0.02**	1.1	0.91	1.4	0.41

HRR=hazard ratio; FDR=first degree relative.

11571 Poster Session

A propensity-score matched analysis for time to trabectedin-failure in advanced myxoid liposarcoma patients.

Roberta Sanfilippo, Silva Ljevar, Andrea Franza, Chiara Fabbroni, Carlo Morosi, Angelo Paolo Dei Tos, Alessandro Gronchi, Dario Callegaro, Rosalba Miceli, Paolo Giovanni Casali; Adult Mesenchymal and Rare Tumor Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Unit of Biostatistics for Clinical Research, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Department of Radiology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; Department of Medicine (DIMED), Surgical Pathology & Cytopathology Unit, University of Padua, Padua, Italy; Sarcoma Service - Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Whether to discontinue trabectedin (T) in soft-tissue sarcoma (STS) patients (pts) with response or stable disease remains controversial. In 2015, the T-DIS trial (Le Cesne et al., Lancet Oncology) showed a progression-free survival (PFS) benefit for T-maintenance after six cycles in STS patients. However, myxoid liposarcoma (MLPS) show a unique sensitivity to T, likely due to its specific mechanism of action. We retrospectively evaluated a "stop-and-go" strategy, in terms of time to treatment (T) failure (TTF) and overall survival (OS) in advanced MLPS pts. **Methods:** We carried out a retrospective analysis of 79 MLPS pts treated with T at our institution from September 2002 to December 2024. Inclusion criteria required pts to be progression-free (per RECIST) after 6 cycles of T. TTF was defined as the time from the 6th cycle to secondary resistance to T or death, whichever occurred first. Statistical methods included Kaplan-Meier survival analysis and propensity-score matched Cox proportional hazards models (weighted and unweighted) with time-dependent variables. **Results:** 60 MLPS pts were eligible for analysis (median age: 48 years, IQR: 39–57; 37 males, 23 females). Of these, 27 (34%) pts were treated with a "stop-and-go" strategy, discontinuing T after achieving radiological response or disease stability. T was discontinued at a median of 12 cycles (range: 6-28). Median follow-up was 56.9 months (IQR: 28.1–112.5), with a median TTF of 51.4 months (95% CI: 37.1– NA) in the "stop-and-go" group versus 10.0 months (95% CI: 6.6–17.7) in the T-maintenance group. OS was 55 months (95% CI 38.5 - NA) vs 23 months (95% CI 21-27.9) in the two groups, respectively. Weighted Cox models predicted an HR of 0.32 (95% CI: 0.11–0.93) for TTF and of 0.28 (95% CI 0.07 – 1.12) for OS, thus favoring the stop-and-go approach. Additional factors, including ECOG performance status (PS), age, primary tumor site, and surgery post-T discontinuation, were adjusted in the analysis. **Conclusions:** Our findings raise the question whether a "stop-and-go" strategy with T is the best option in the subset of MLPS pts. How to test further this hypothesis in such a rare subset, and which predictive factors may optimize the approach, is questionable. Research Sponsor: None.

11572 Poster Session

Moving beyond the traditional two-step approach for prognosis prediction: The BayeSarc model.

Gabriele Tine', Dario Callegaro, Sandro Pasquali, Jay Wunder, Peter Charles Ferguson, Anthony M Griffin, Dirk C. Strauss, Andrew J. Hayes, Sylvie Bonvalot, Dimitri Tzanis, Toufik Bouhadiba, Paolo G. Casali, Alessandro Gronchi, Rosalba Miceli; Biostatistics for Clinical Research, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Molecular Pharmacology, Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy; Department of Surgical Oncology, Princess Margaret Cancer Centre and Department of Surgery, Mount Sinai Hospital, Toronto, ON, Canada; Mt Sinai Hospital, Toronto, ON, Canada; Mount Sinai Hospital-Breast Medical Oncology, Toronto, ON, Canada; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Institut Curie, Paris, France; Digestive Surgery Department, Gustave Roussy Institut, Villejuif, France; Institut Curie, Milan, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Sarcoma Service - Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Unit of Biostatistics for Clinical Research, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Extremity Soft tissue sarcomas (eSTS) are rare and heterogeneous, limiting the collection of large datasets for robust predictive modeling. Sarculator, a Cox model-based tool for overall survival (OS) prediction, was built using the traditional two-step paradigm (1) model building and (2) external validation. However, this method can underperform on external cohorts, often yielding low predictive accuracy and limited generalizability. We introduced a Bayesian Sequential Learning strategy to iteratively refine Sarculator, incorporating new data while preserving prior properties. **Methods:** The initial model was built on the Italian Sarculator development cohort, with age, tumor size, tumor grade, and histology as covariates. Sequential updates were then performed with the three original Sarculator external validation cohorts , and a more recent Italian cohort. Each step used the results from the previous update as prior information for the next. Performance was assessed as discriminative ability (C-index) and calibration. Key differences from the original Sarculator were Bayesian Cox modelling, and a piecewise-constant hazard. **Results:** The two-step approach yields separate performance metrics for each cohort, making generalizability unclear when performance drops (e.g. French cohort, Table). Conversely, the sequential approach progressively increases the total information (number of patients and follow-up), without discarding previous evidence, and readjusts performance metrics at each step. Occasional declines in the C-index reflect cohort-specific divergences but can be reversed in subsequent updates if newer cohorts share similar features. Ultimately, the final BayeSarc outperformed the initial model in discriminative ability, calibration, and reduced uncertainty in predictions. **Conclusions:** BayeSarc is an accurate, generalizable OS prediction model for eSTS, preserving external validation properties while moving beyond the conventional two-step approach. By building on prior evidence, the model dynamically adapts over time, ultimately relying on 4713 patients, with results independent of cohort order. BayeSarc sets a benchmark for future rare-disease prognostic research, paving the way for incorporating new cohorts and/or prognostic variables (e.g. emerging biomarkers).
Research Sponsor: None.

Cohorts	Istituto Nazionale Tumori, Milan, Italy 1994-2013	Mount Sinai Hospital, Toronto, Canada 1994-2013	Royal Marsden Hospital, London, UK 2006-2013	Institut Gustave Roussy, Villejuif, France 1996-2012	Istituto Nazionale Tumori, Milan, Italy 2014-2021
Two-step procedure	Dev N=1452	Val 1 N=1436	Val 2 N=440	Val 3 N=420	Val 4 N=965
C-index	0.767	0.775	0.762	0.698	0.765
Bayesian updating	**Dev** N=1452	**Upd 1** N=2888	**Upd 2** N=3228	**Upd 3** N=3748	**Upd 4** N=4713
C-index	0.761	0.775	0.771	0.707	0.796

11573 Poster Session

Clinical and prognostic implications of the TCR repertoire in leiomyosarcoma.

John Seng Wang, Rusul Al-Marayaty, Juliana Ng, Meghan Maureen Lynch, Nourhane Al Akoum, Farres Obeidin, Jian-Jun Wei, Demirkan Gursel, Borislav A. Alexiev, Akhil Chawla, Jeffrey D. Wayne, Vinai Gondi, John P. Hayes, Fahad Ahmed Faruqi, Terrance Peabody, Samer Attar, Pedro Antonio Hermida de Viveiros, Seth Pollack; Northwestern University Feinberg School of Medicine, Chicago, IL; Medstar Washington Hospital Center, Department of Medicine, Washington, DC; Department of Medicine, Division of Hematology and Oncology, Northwestern University, Chicago, IL; Department of Pathology, Northwestern University, Chicago, IL; Department of Surgery, Division of Surgical Oncology, Northwestern University, Chicago, IL; Department of Radiation Oncology, Northwestern University, Chicago, IL; Department of Orthopaedic Surgery, Northwestern University, Chicago, IL

Background: Leiomyosarcomas (LMS) are aggressive mesenchymal tumors sometimes classified by primary location as uterine LMS (uLMS) versus extra-uterine LMS (eLMS). In pursuit of novel therapies, study of the tumor microenvironment and the repertoire of T-Cell Receptor (TCR) sequences from infiltrating T-lymphocytes could help guide the application of immunotherapy in LMS. Herein, we explore the first ever database of TCR-sequenced LMS tumors in one of the larger LMS cohorts analyzed to date. **Methods:** A single-institution retrospective study was performed including 117 adult patients with pathology-confirmed LMS diagnosed between 1998 and 2022 at Northwestern Medicine. Overall survival (OS), progression free survival (PFS), and relapse free survival (RFS) were analyzed using Kaplan-Meier Curves (GraphPad Prism). DNA was extracted from 61 eLMS and 39 uLMS formalin-fixed paraffin-embedded (FFPE) blocks using Qiagen's AllPrep DNA/RNA FFPE kit and used for TCR sequencing. **Results:** 117 patients who met the inclusion criteria were classified as uLMS (n=54) and eLMS (n=63). Baseline patient demographics and disease characteristics are described in the table. Median OS significantly differed between uLMS and eLMS patients (559 versus 1548 days; p=0.001). Median PFS was not statistically different between metastatic uLMS versus eLMS (142 versus 159 days; p=0.63). Median RFS was not significantly different between localized uLMS versus eLMS (283 versus 429 days; p=0.30). The number of different TCR clones amongst TCRs was significantly different between the two tumor types: uLMS demonstrated a mean of 821 clones versus 2415 clones in eLMS (p=0.005). Mean CDR3 length in uLMS tumors was 47.9 (95% CI 46.53-49.25) versus 48.45 (95% CI 46.66-50.25) in eLMS tumors (p=0.10). TRBV20 was the most common gene in uLMS cases and the second most common gene in eLMS cases. **Conclusions:** This study provides the first analysis of the TCR repertoire in LMS patients and the largest analysis of TCR repertoire ever reported in any sarcoma subtype. eLMS tumors contained significantly more TCR clones than uLMS tumors. CDR3 did not significantly differ between cohorts, and the TRBV20 gene was frequently identified in both LMS subtypes. Further gene expression analysis and immunohistochemistry is currently underway. As might be expected, clinical outcomes were worse for uLMS including significantly lower OS. Updated data will be presented including additional information about the TCR repertoire as well as gene expression data to contextualize these findings. Research Sponsor: None.

Baseline patient demographics and disease characteristics.

	uLMS (n=54)	eLMS (n=63)
Median Age (range)	55 years (25-91)	58 years (23-87)
Female Sex: n (%)	54 (100%)	34 (54%)
Median Tumor Size (range)	11 cm (1-34)	5 cm (0.7-25)
Necrosis Present: n (%)	47 (87%)	33 (52%)
Positive Margins: n (%)	5 (9%)	9 (14%)
Stage IV Disease: n (%)	16 (30%)	5 (8%)
Adjuvant Chemotherapy: n (%)	27 (50%)	4 (6%)

Ramucirumab in pediatric and young adult patients (Pts) with relapsed/refractory (R/R) desmoplastic small round cell tumor (DSRCT) or synovial sarcoma (SS): Results from the CAMPFIRE study.

Emily K. Slotkin, Michela Casanova, Brian Andrew Van Tine, Sandra J. Strauss, Spyridon Gennatas, Ayumu Arakawa, Julia C. Chisholm, Claudia Valverde, Alexia Francesca Bertuzzi, Alok Kothari, Martin McCabe, Simone Hettmer, Theodore Willis Laetsch, Uta Dirksen, Utako Oba, Uwe R. Kordes, Adams Kusi Appiah, Kamnesh R. Pradhan, Andrea Ferrari, CAMPFIRE Study Team; Memorial Sloan Kettering Cancer Center, New York, NY; Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy; Washington University School of Medicine, St. Louis, MO; University College London Hospital NHS Trust, London, United Kingdom; Guy's and St Thomas' NHS Foundation Trust and Sarcoma Unit, Royal Marsden and Institute of Cancer Research, London, United Kingdom; Department of Pediatric Oncology, National Cancer Center Hospital, Tokyo, Japan; The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Vall d'Hebron University Hospital, Barcelona, Spain; Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center-IRCCS, Rozzano, Italy; Center for Cancer and Blood Disorders, Phoenix Children's Hospital, Phoenix, AZ; The Christie NHS Foundation Trust, Manchester, United Kingdom; Division of Pediatric Hematology and Oncology, Department of Pediatric and Adolescent Medicine, Freiburg, Germany; Division of Oncology, Children's Hospital of Philadelphia, and Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Essen University Hospital, Essen, Germany; Department of Pediatrics, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan; Department of Pediatric Hematology and Oncology, University Medical Center Eppendorf, Hamburg, Germany; Eli Lilly and Company, Indianapolis, IN; Eil Lilly and Company, Indianapolis, IN; Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy

Background: Few effective therapies exist for pts with R/R DSRCT and SS, and hence, their prognosis remains poor. Preclinical data suggested the relevance of vascular endothelial growth factor receptor 2 (VEGFR2) inhibition in these diseases. We evaluated the efficacy of ramucirumab (RAM, VEGFR2 receptor antagonist) + chemotherapy vs. chemotherapy alone in pediatric and young adult pts with R/R DSRCT (JV01) or SS (JV02). **Methods:** JV01 and JV02 were randomized, global, multicenter, Phase 1/2 studies in pts aged ≤29 years with R/R DSRCT or SS and evaluated pts treated with RAM + cyclophosphamide/vinorelbine (CV; JV01) and RAM + gemcitabine/docetaxel (GD; JV02). Pts were randomized 2:1 to the experimental and control groups. The primary endpoint was progression-free survival (PFS) per RECIST v1.1, analyzed via a Bayesian hierarchical model allowing adaptive borrowing on effect size (log hazard ratio [HR]) between JV01 and JV02 and control arm augmentation with historical (real world) data. Interim futility required a probability (Pr) of PFS (HR < 1) $> 60\%$, and intervention success at final analysis was declared at Pr $> 99\%$. Frequentist analysis (1-sided $\alpha = 0.1$) was performed as a sensitivity analysis. Safety was a secondary endpoint. **Results:** Baseline characteristics were balanced between the treatment arms in both studies: RAM+CV, n = 20; CV, n = 10; RAM+GD, n = 16; GD, n = 7. JV02 met the futility criterion (Table) and was suspended without completing enrollment. JV01 fully enrolled but did not meet the primary endpoint at the final analysis (PFS HR = 0.7, 98% credible interval = 0.3, 1.7; pr [HR < 1] = 86.4% vs. 99%). However, frequentist analysis in JV01 showed that pts in the RAM+CV arm had a numerical improvement of 5 months in median PFS vs. the CV arm. Overall, no significant safety events were reported in either study. **Conclusions:** The PFS outcome was not met for either rare disease. The numerical trend in JV01 is noteworthy, especially considering the limited treatment options available for DSRCT. Safety was consistent with the known profiles of the individual treatments and the population. Clinical trial information: NCT04145700, NCT04145349. Research Sponsor: Eli Lilly and Company.

	JV01			JV02		
	RAM+CV (n=20) Median PFS (months), 98% CrI[a]	CV (n=10)	HR (80% CrI)[b]	RAM+GD (n=16) Median PFS (months), 98% CrI[a]	GD (n=7)	HR (80% CrI)[b]
Primary Bayesian Analysis	5.7 (3.2, 10.0)	3.7 (1.8, 8.3)	0.7 (0.3, 1.7) Pr (HR <1) = 86.4 %	3.7 (1.5, 11.5)	6 (2.1, 18.0)	1.8 (0.8, 3.1) Pr (HR <1) = 20.1%
PFS events, n	16	8		9	5	
Frequentist Analysis[c]	6.8 (5.5, 10.4)	1.7 (1.4, 2.7)	0.5 (0.3, 0.8) p = 0.082	2.1 (1.9, 6.1)	2.0 (1.4, NR)	0.7 (0.3, 1.5) p = 0.544

CI = confidence interval; CrI = credible interval; CV = cyclophosphamide/vinorelbine; GD = gemcitabine/docetaxel; HR = hazard ratio; NR = not reached; PFS = progression-free survival; Pr = probability; RAM = ramucirumab.
[a]Posterior median.
[b]Posterior mean displayed.
[c]80% CI for JV01 and JV02.

11575 Poster Session

Global inequities in sarcoma clinical trials: A comprehensive analysis over the last decade.

Shushan Hovsepyan, Karen Bedirian, Amalya Sargsyan, Elen Baloyan, Vahe Khachatryan, Aharon Tsaturyan, Stella Ghevondyan, David Khanoyan, Mirna Antabian, Swati Bhayana, Jack Yacoubian, Gevorg Tamamyan; Yerevan State Medical University, Immune Oncology Research Institute, Yerevan, Armenia; Yeolyan Hematology and Oncology Center, Immune Oncology Research Institute, Yerevan, Armenia; Adult Solid Tumor and Chemotherapy Clinic, Yeolyan Hematology and Oncology Center, Yerevan, Armenia; Yerevan State Medical University, Immune Oncology Research Institute, Yeolyan Hematology and Oncology Center, Yerevan, Armenia; Flushing House Medical Center, Internal Medicine Department, New York, NY; Yerevan State Medical University, Yerevan, Armenia; University of California San Diego, San Diego; British International School of Armenia, Yerevan, Armenia; Yerevan State Medical University, Yerevan, Armenia, Armenia; Fortis Memorial Research Institute, Gurugram, India

Background: Sarcomas are rare, comprising 15% of childhood cancers and 1% of adult cancers, yet survival rates remain poor. The overall 5-year survival for soft tissue sarcomas (STS) is 65%, dropping from 81% for localized disease to just 16% for metastatic cases. For bone sarcomas, survival declines from 84% at localized stages to 31% for metastatic cases. This highlights the critical need for novel therapies and equitable research access. To address this, the current review discusses sarcoma clinical trials conducted over the past decade. **Methods:** Sarcoma-related clinical trials registered on ClinicalTrials.gov from 2016 to 2025 were analyzed. Variables included study status, conditions, phases, randomization, dates, country, age groups, sample size, sponsor, and reasons for discontinuation. Geographic data were categorized by World Bank income levels. Descriptive statistics summarized key characteristics. **Results:** Out of 1,232 studies, 65% were focused exclusively on sarcomas. Alarmingly, only 0.4% of the studies were conducted in low-income countries (LICs) and only 18% in low- and middle-income countries (LMICs), underscoring a profound underrepresentation of these regions in sarcoma research. Recruitment status varied, with 39% of trials actively recruiting, 18% completed, and 14% terminated—predominantly due to challenges in participant accrual. Early-phase trials predominated, comprising 34% in phase 1 and phase 1/2, and 30% in phase 2. Late-phase and post-marketing studies were sparse, representing only 5%. Interventional trials accounted for 82% of the total, though most lacked randomization. The majority of studies (72%) were academia-sponsored trials. Only 1% of studies were exclusively dedicated to pediatric populations, while 36% included both adults and children, and 63% enrolled adults exclusively. The median sample size was 46 participants (IQR 22–117), and the median study duration was 47 months (IQR 29–70). There are no trend changes in the number of studies that were launched from 2016 to 2024. **Conclusions:** Our study highlights inequities in the geographic distribution of sarcoma trials, and the substantial neglect of LICs and pediatric populations. This underscores an urgent need for global efforts to address these disparities and enhance inclusivity in clinical research.
Research Sponsor: None.

11576 Poster Session

NF1- and non-NF1–associated malignant peripheral nerve sheath tumors (MPNST): The University of Texas MD Anderson (MDACC) experience.

Reeja Raj, Reshma Vilson, Cissimol Joseph, Heather Y. Lin, Pujita Munnangi, Prapassorn Thirasastr, Michael S. Nakazawa, Keila E. Torres, Dejka M. Araujo, Robert S. Benjamin, Anthony Paul Conley, J. Andrew Livingston, Joseph Aloysius Ludwig, Shreyaskumar Patel, Ravin Ratan, Vinod Ravi, Maria Alejandra Zarzour, Elise F. Nassif Haddad, Neeta Somaiah; The University of Texas MD Anderson Cancer Center, Houston, TX; UNTHSC, Fort Worth, TX; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; Texas A&M University, College Station, TX; Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: MPNSTs are aggressive sarcomas with poor prognosis due to their high propensity for metastasis, rapid growth and limited response to standard chemotherapy (CT). While commonly associated with neurofibromatosis type 1 (NF1), they can also occur sporadically (non-NF1). This study aims to evaluate baseline characteristics and outcomes in NF1 and non-NF1 associated MPNST in order to understand CT effectiveness and set a benchmark for future therapies. **Methods:** A retrospective chart review was conducted at MDACC, including 258 patients diagnosed with MPNST (173 NF1 and 85 non-NF1). Data collected included demographic information, primary tumor location and size, disease stage at diagnosis (localized vs. metastatic), efficacy of CT regimens utilized, and survival data. Descriptive statistics were used to summarize patient characteristics. Chi squared tests or Fisher's exact tests, and t-test/ANOVA were used to compare patient's characteristics and distributions of overall survival (OS), and progression-free survival (PFS) were estimated by the Kaplan-Meier method. **Results:** Median age at diagnosis was 33 yrs (IQR 22-44) and 50 yrs (IQR 38-61), and median tumor size at diagnosis 7.4cm and 6.3cm for the NF1 and non-NF1 cohorts, respectively. Tumors were most commonly located in the trunk, followed by the lower extremity, with head and neck involvement more frequent in non-NF1 cases. Metastatic disease was present at diagnosis in 28.3% of NF1 (49/173) and 22.4% (19/85) of non-NF1 cases. Adriamycin with Ifosfamide (AI) was the most utilized first-line CT regimen while gemcitabine plus docetaxel was the preferred second-line regimen. 154 patients, 87 patients, and 37 patients received frontline, second-line, and third-line CT, respectively. Median PFS for front-line CT was 8.0 months (4.7, NR) for patients with metastatic disease at presentation and 11.7 months (8.94, NR) for patients who received AI. Median OS was 2.34 yrs (1.88, 3.15) vs 1.81 yrs (0.89, 3.76) for NF1 and non-NF1 cohorts ($p = 0.038$), respectively. 5-yr OS was 42% (33, 51) for local disease and 9% (3, 19) for metastatic disease at presentation. Additional analysis of PFS by NF1 status, lines of therapy, and regimen will be presented at the conference. **Conclusions:** Patients with metastatic MPNST have dismal outcomes and CT efficacy and utilization drops after frontline treatment. These findings highlight the importance of early diagnosis and tailored novel therapeutics for MPNST patients. Research Sponsor: None.

11577 Poster Session

Enhancing soft tissue sarcoma surveillance: The role of ctDNA testing in early detection and monitoring beyond traditional imaging.

Amrit Paudel, Osvaldo Nunez Jr., Chinmay Jani, Brandon Edward Rose, Akshee Batra, Priya Chattopadhyay, Palash Asawa, Alissette Naveda, Steven Bialick, Gina Z. D'Amato, Jonathan C. Trent, Emily E. Jonczak; University of Miami Sylvester Comprehensive Cancer Center/Jackson Health System, Miami, FL; University of Miami Miller School of Medicine, Miami, FL; University of Miami Sylvester Comprehensive Cancer Center/Jackson Memorial Hospital, Miami, FL; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Department of Internal Medicine, University of Miami/Jackson Memorial Hospital, Miami, FL; University of Miami Sylvester Comprehensive Cancer Center, Hialeah, FL

Background: Soft tissue sarcoma (STS), particularly large (>5 cm), intermediate to high grade, and aggressive subtypes, is associated with high relapse rates, necessitating effective surveillance. Traditional methods, including physical exams and radiologic imaging, can be inconclusive, leading to radiation exposure. Circulating tumor DNA (ctDNA), a biomarker from tumor-derived cell-free DNA in the bloodstream, offers a potential solution for early recurrence detection and treatment monitoring. While ctDNA has shown promise in various cancers, its role in STS remains under-explored. **Methods:** We conducted a retrospective analysis of localized, high-risk STS patients who underwent surgery, followed by standard imaging, physical exams, and Signatera ctDNA testing from April 2023-January 2025. The study evaluated the concordance between ctDNA positivity and imaging findings, with a subgroup analysis exploring metastatic patterns and molecular profiles in ctDNA-positive patients. Mann-Whitney test was conducted to evaluate the difference in time to progression between ctDNA and imaging. **Results:** The cohort consisted of 63 STS patients, including 501 plasma samples for Signatera ctDNA testing alongside routine imaging. The patient population was 52% female, 35% Hispanic, and 80% White. ctDNA assay was performed on an average of 8 ± 4 plasma samples per patient, over a median surveillance duration of 12 months. Of the 63 patients, 18 tested positive for ctDNA. There was no significant difference (p=0.984) in the time to progression between ctDNA testing (35 ± 17.6 months) and radiological imaging (34.3 ± 18.5 months). Our data also revealed that all patients with negative ctDNA results had corresponding negative imaging findings. In the subgroup analysis of ctDNA-positive patients, majority had pulmonary metastasis (7, 39%), followed by liver metastasis (3, 16%). Molecular profiling demonstrated significant heterogeneity, with TP53 mutations being the most common alteration, present in 4 (22%) patients. **Conclusions:** Our study demonstrates the potential utility of ctDNA testing in monitoring high-risk STS patients. ctDNA showed no significant difference in time to progression compared to traditional imaging and offers a non-invasive alternative with strong concordance with imaging results, particularly for patients with negative ctDNA findings. These findings underscore the potential of ctDNA as a complementary tool to traditional surveillance methods, potentially reducing reliance on radiologic imaging and enhancing personalized treatment strategies. Research Sponsor: None.

Most common STS subtypes and ctDNA positivity.

STS subtypes	Total number of patients	Positive ctDNA testing (%)
Leiomyosarcoma	15	5 (33.3)
Synovial Sarcoma	7	2 (28)
Liposarcoma	5	3 (60)
Myxofibrosarcoma	4	0 (0)
Fibroblastic	4	1(25)
Pleomorphic	3	1(33.3)
Angiosarcoma	3	1(33.3)
Others	22	5(22)

TPS11578 Poster Session

Phase 1a/1b study of the safety, pharmacokinetics, and antitumor activity of ziftomenib in combination with imatinib in patients with advanced gastrointestinal stromal tumors (GIST) after imatinib failure.

Mrinal M. Gounder, Shreyaskumar Patel, Jason K. Sicklick, Mark Agulnik, Suzanne George, Margaret von Mehren, Xiaoxian Dai, Amitava Mitra, Xiaoyan Yang, Ramya Antony, Blake Tomkinson, Daniel Corum, Mollie Leoni, Tom Kozlek; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical School, New York, NY; University of Texas MD Anderson Cancer Center, Houston, TX; University of California San Diego Moores Cancer Center, La Jolla, CA; Keck School of Medicine of University of Southern California, Los Angeles, CA; Dana-Farber Cancer Institute, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; Kura Oncology, Inc., San Diego, CA

Background: GIST is the most common mesenchymal neoplasm of the digestive tract and is mainly driven by gain-of-function oncogenic mutations in the receptor tyrosine kinase KIT. Patients with GIST are typically treated with anti-KIT tyrosine kinase inhibitors (TKIs) such as imatinib. However, few patients achieve a complete response, and most eventually progress due to secondary alterations in *KIT* that cause resistance to therapy. Additional TKIs are approved in later lines but have shown only moderate clinical outcomes, highlighting the need for additional therapeutic approaches. Preclinical studies have shown that the menin-KMT2A complex epigenetically upregulates *KIT* expression in GIST cells. Ziftomenib is a potent and highly selective menin inhibitor that disrupts formation of the menin-KMT2A complex. Ziftomenib plus imatinib has demonstrated synergistic antitumor activity in imatinib-sensitive and -resistant GIST models, with reduced KIT protein levels and downstream oncogenic signaling observed in imatinib-resistant GIST patient-derived xenografts treated with the combination. Together, ziftomenib plus imatinib may enhance KIT recycling while reducing *KIT* transcription. This combination is currently being investigated clinically in patients with imatinib-sensitive and -resistant advanced GIST. **Methods:** KOMET-015 (NCT06655246) is a phase 1a/1b, open-label study to determine the safety, tolerability, recommended phase 2 dose (RP2D), and preliminary antitumor activity of ziftomenib plus imatinib (400 mg) for advanced/metastatic GIST. KOMET-015 includes dose-escalation, RP2D determination, and dose-expansion parts. Eligible patients (≥18 yrs) must have a biopsy-proven diagnosis of advanced/metastatic *KIT*-mutant GIST (T670X excluded) that progressed on imatinib (dose-escalation and RP2D determination parts), with an ECOG PS of ≤2 and measurable disease per modified RECIST (mRECIST). Dose escalation will be based on an i3+3 design to evaluate the safety and tolerability of up to 4 dose levels of ziftomenib combined with imatinib. Based on escalation, up to 2 dose levels will be selected for comparison to determine the RP2D. The dose-expansion part will examine the toxicity and preliminary clinical activity of the RP2D in patients assigned to 1 of 3 cohorts: Cohort A: patients who progressed on imatinib as immediate prior therapy, Cohort B: patients who failed imatinib and had received ≥2 lines of therapy, and Cohort C: imatinib-naive patients. Tumor response will be assessed per mRECIST. All adverse events will be recorded, monitored, and graded based on CTCAE v5.0. The trial is open and actively recruiting with sites in the United States. Clinical trial information: NCT06655246. Enrollment opens Feb 2025. Research Sponsor: Kura Oncology, Inc.

TPS11579 Poster Session

SARC044: A phase II trial of bezuclastinib in combination with sunitinib in patients with GIST who progressed on sunitinib monotherapy.

Candace L. Haddox, Karla V. Ballman, Margaret von Mehren, Michael C. Heinrich, Steven Bialick, Heather Jacene, Hina Shah, Brian D. Crompton, Scott H. Okuno, Jonathan Fletcher, Andrew J. Wagner; Dana-Farber Cancer Institute, Boston, MA; Mayo Clinic, Rochester, MN; Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA; Oregon Health & Science University, Portland, OR; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Dana-Farber Cancer Institute/ Brigham and Women's Hospital, Boston, MA; Division of Medical Oncology, Mayo Clinic, Rochester, MN; Harvard Medical School, Boston, MA

Background: Gastrointestinal stromal tumors (GIST) are commonly driven by mutations in the receptor tyrosine kinase *KIT*. Resistance to approved tyrosine kinase inhibitors (TKIs) arises from additional KIT mutations in the ATP-binding pocket (AP) and activation loop (AL). No single approved TKI broadly suppresses all resistant clones, and overlapping VEGFR inhibition and toxicity limits TKI combinations. The type I TKI bezuclastinib ("BEZ," CGT9486) inhibits KIT AL resistance mutations, does not inhibit VEGFR, and has complimentary activity with sunitinib ("SUN," inhibitor of KIT AP resistance mutations). The first-in-human study (PLX121-01) and ongoing Peak trial (NCT05208047) evaluated BEZ+SUN showing promising safety and efficacy in GIST. SARC044 investigates BEZ+SUN in patients (pts) with SUN-resistant, KIT-mutant GIST, and correlatives aim to determine mechanisms of response and resistance (NCT06208748). **Methods:** SARC044 is a multi-center, open label, single-arm phase II trial enrolling up to 40 adult pts with KIT exon 9 or 11-mutant GIST resistant to imatinib and SUN. After TKI washout (baseline, "b/l"), pts initiate BEZ 600 mg daily for 2 weeks, then add SUN 37.5 mg daily, taking both drugs continuously (28-day cycles) until mRECISTv1.1 progression or unmanageable toxicity. Response evaluations (RE) are performed every 8 weeks (wk) through 15 months (mo) on study, then every 12 wk. Circulating tumor DNA (ctDNA) is collected at b/l, cycle 1 day 15 (C1D15), C2D1, C3D1, and progression. Targeted exome sequencing (TES) of ctDNA will track primary/resistant KIT mutation dynamics across therapy. ^{18}FDG PET/CTs are performed in 20 pts at b/l, C1D15, and C2D1, which guide a biopsy of a resistant tumor. TES, allele-specific and long-read PCR (to detect AP+AL mutation phasing), and immunoblotting (evaluating KIT pathway activation) will be performed on tissue. EORTC QLQ-C30 surveys collect pt-reported outcomes (PRO) at b/l, on treatment, and at progression. The primary endpoint is median progression-free survival (mPFS) and secondary endpoints include overall survival at 1 and 2 years, clinical benefit rate at 16 wk, adverse event rate, PRO, and KIT mutation profile in ctDNA and tissue. 35 evaluable pts achieves 83% power ($p<0.05$, one-sided) in a one-sample log-rank test to detect a mPFS of 6.5 mo vs 4 mo (historic control). Expected accrual is 12 mo across 4 sites in the United States with ~36 mo to study completion. Clinical trial information: NCT06208748. Research Sponsor: Cogent Biosciences; Life Raft Group; Brown Family Fund; Conquer Cancer©, the ASCO Foundation.

TPS11580 **Poster Session**

An open-label phase 1/2 study of DCC-3009 monotherapy in patients with advanced gastrointestinal stromal tumor.

Sreenivasa R. Chandana, Suzanne George, Ping Chi, Scott H. Okuno, Steven Attia, Alessandra Maleddu, Jonathan C. Trent, Adam Burgoyne, Vicki Leigh Keedy, Vandy Black, Bo King, Anna Papinska, Elma Feric Bojic, Ying Yuan, Frederic J. Reu, Matthew L. Sherman, Michael S. Gordon; START Midwest, The Cancer & Hematology Centers, Grand Rapids, MI; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY; Mayo Clinic, Rochester, MN; Mayo Clinic, Jacksonville, FL; Department of Medicine, University of Colorado School of Medicine, Aurora, CO; Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL; University of California San Diego Moores Cancer Center, San Diego, CA; Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN; Deciphera Pharmaceuticals, LLC, Waltham, MA; HonorHealth Research Institute, Scottsdale, AZ

Background: Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the gastrointestinal tract. *KIT* and platelet-derived growth factor receptor α (*PDGFRA*) mutations remain the key oncogenic drivers in the majority of patients with advanced GIST, with acquired secondary drug-resistant mutations contributing to the heterogeneity and complexity of the disease. The diversity of these resistance mutations allows escape from standard-of-care tyrosine kinase inhibitor (TKI) therapy, creating an unmet need for novel therapies that inhibit all clinically relevant GIST-driving mutations. DCC-3009 is an investigational, highly potent, and selective switch-control KIT and PDGFRA inhibitor designed to act against known clinically relevant primary and secondary GIST-driving mutations while limiting off-target effects. Preclinical data showed that DCC-3009 has strong antitumor effects in xenograft models driven by resistant *KIT* mutations, optimized solubility and oral bioavailability, and low risk of cytochrome P450 inhibition. Here, we describe an ongoing phase 1/2 study evaluating DCC-3009 as a monotherapy in patients with advanced GIST. **Methods:** This study is a multicohort, open-label, phase 1/2 trial evaluating the safety, tolerability, and efficacy of DCC-3009 in patients with advanced GIST (NCT06630234). This trial uses a modular approach, with each module defined according to the therapy (DCC-3009 alone or in combination with other anticancer agents) and divided into 2 parts (dose escalation and dose expansion). For inclusion in the DCC-3009 monotherapy dose escalation, adult patients ($\geq$18 years) must have histologically or cytologically confirmed advanced GIST with documented *KIT* or *PDGFRA* mutation and progression on or intolerance to at least 1 approved TKI regimen in the advanced setting (imatinib if *KIT*-mutant). Patients must have at least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST v1.1) and an Eastern Cooperative Oncology Group Performance Status of 0 or 1 at screening. Exclusion criteria include receiving systemic anticancer therapy (encompassing investigational agents) within 14 days or less than 5 half-lives, radiotherapy within 14 days prior to first dose of study drug, prior or concurrent malignancy requiring treatment or expected to need treatment for active cancer, known allergy or hypersensitivity to the study drug components or any of its excipients, and impaired oral absorption or malabsorption syndrome. Enrolled patients across monotherapy dose escalation will receive DCC-3009 orally in 28-day cycles. The primary outcome measures for monotherapy dose escalation include safety assessment. Secondary outcome measures include objective response rate, duration of response, and progression-free survival by mRECIST v1.1, as well as overall survival and pharmacokinetics. Clinical trial information: NCT06630234. Research Sponsor: Deciphera Pharmaceuticals, LLC.

PYNNACLE phase 2 clinical trial of rezatapopt in patients with advanced solid tumors harboring a *TP53* Y220C mutation.

Alison M. Schram, Jean-Sebastien Frenel, Melissa Lynne Johnson, Antoine Italiano, Shivaani Kummar, Andrew L. Coveler, Alexander I. Spira, Amy Body, Elisa Fontana, Elena Garralda, Alastair Greystoke, Michael Millward, Giovanni Scambia, David Shao Peng Tan, Marc Mardoche Fellous, Ecaterina Elena Dumbrava, Gilberto Lopes; Memorial Sloan Kettering Cancer Center, New York, NY; Institut de Cancerologie de L'Ouest, Saint-Herblain, France; Sarah Cannon Research Institute, Nashville, TN; Drug Development Department (DITEP), Gustave Roussy, Villejuif, France; Knight Cancer Institute, Portland, OR; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; NEXT Oncology Virginia, Fairfax, VA; Monash Medical Centre, Monash Health, Clayton, Australia; Sarah Cannon Research Institute UK, London, United Kingdom; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Newcastle Upon Tyne Hospital NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; Linear Clinical Research Ltd and School of Medicine, University of Western Australia, Perth, Western Australia, Australia; Fondazione Policlinico Universitario A. Gemelli, IRCCS, Division of Gynecologic Oncology, Catholic university of the Sacred Heart, Rome, Italy; National University Cancer Institute, Singapore, Singapore; PMV Pharma, Cranbury, NJ; Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: *TP53*, encoding p53 protein, is one of the most frequently mutated genes across all cancers, with TP53 mutations found in ~59% of all solid tumors. *TP53* mutations result in the loss of p53 tumor suppressor functions leading to tumor development and progression. The *TP53* Y220C mutation, occurring in ~1% of all solid tumors, is a missense mutation that destabilizes the p53 protein. Rezatapopt (also known as PC14586) is an investigational, first-in-class, selective, p53 reactivator specific to the *TP53* Y220C mutation that restores wildtype p53 function. Preliminary findings from Phase 1 part of the PYNNACLE (NCT04585750) Phase 1/2 study, showed that rezatapopt had a favorable safety profile and single-agent efficacy in heavily pre-treated patients with solid tumors harboring a *TP53* Y220C mutation (*Schram A, AACR-NCI-EORTC 2023, LBA25*). Here we describe the study design for the registrational Phase 2 part of the PYNNACLE study. **Methods:** The Phase 2 part of PYNNACLE is an ongoing, global, single-arm, open-label, multicenter basket trial in patients with solid tumors harboring a *TP53* Y220C mutation (Table). Patients must have measurable disease at baseline, ECOG performance status 0 or 1, and adequate organ function; other key inclusion criteria are listed in the table. Patients with *KRAS* single nucleotide variants, primary CNS tumors and unstable brain metastases are excluded. Eligible patients receive rezatapopt 2000mg, orally, once daily, taken with food, for continuous 21-day cycles. Patients are followed until death, lost to follow-up, two years after last patient discontinuation, or end of study. As of March 2024, ≈114 patients are planned to be enrolled. Clinical trial information: NCT04585750. Research Sponsor: PMV Pharmaceuticals, Inc.

PYNNACLE Phase 1/2 basket study (NCT04585750).

Patient population N≈114 (planned)	Key inclusion criteria	Primary endpoints	Secondary endpoints
Cohort 1 **Ovarian cancer (platinum-resistant)** **n≈42** **Cohort 2** **Lung cancer** **n≈18** **Cohort 3** **Breast cancer** **n≈18** **Cohort 4** **Endometrial cancer** **n≈18** **Cohort 5** **Other solid tumors** **n≈18**	· Adults aged ≥18 years (all global sites except ≥21 years in Singapore) · Adolescents aged 12–17 years if weight ≥40 kg (90 lbs; Australia, South Korea and USA only) · Locally advanced or metastatic solid tumors · Documented *TP53* Y220C mutation and *KRAS* wildtype* · Prior standard therapy or ineligible for appropriate standard of care therapy	· ORR per BICR assessment (RECIST v1.1) across all cohorts · ORR per BICR assessment (RECIST v1.1) in ovarian cancer cohort	· ORR per investigator assessment (RECIST v1.1) across all cohorts and the ovarian cancer cohort · Time to response, duration of response, disease control rate · Progression-free survival · Overall survival · Safety · Pharmacokinetics · Quality of life

*Defined as no *KRAS* single nucleotide variant.
BICR, blinded independent central review; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1.

TPS11582 Poster Session

Phase 3 study of ivosidenib vs placebo in locally advanced or metastatic IDH1-mutant conventional chondrosarcoma untreated or previously treated with 1 systemic treatment regimen (CHONQUER).

Andrew J. Wagner, Silvia Stacchiotti, Channa Debruyne, Abdulazeez Salawu, Jean-Yves Blay, Fernando Augusto Batista Campos, Hiroaki Hiraga, Antoine Italiano, Akira Kawai, Ganessan Kichenadasse, Yoshihiro Nishida, Seth Pollack, Zhe Qu, Evinaa Sellaiah, Ilona Tala, Gabriel Tinoco, Jonathan C. Trent, Karina Costa Maia Vianna, Kan Yonemori, William D. Tap; Dana-Farber Cancer Institute, Boston, MA; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Servier International Research Institute, Brussels, Belgium; Division of Medical Oncology, Mount Sinai Hospital, Sinai Health, University of Toronto, Toronto, ON, Canada; Centre Léon Bérard, Lyon, France; A.C. Camargo Cancer Center, São Paulo, Brazil; Department of Musculoskeletal Oncology, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan; Institut Bergonié, Bordeaux, France; Department of Musculoskeletal Oncology and Rehabilitation, National Cancer Center Hospital, Tokyo, Japan; College of Medicine and Public Health, Flinders University, Adelaide, Australia; Nagoya University Hospital, Nagoya, Japan; Department of Medicine, Division of Hematology and Oncology, Northwestern University, Chicago, IL; Servier BioInnovation, Boston, MA; Servier International Research Institute, Gif-Sur-Yvette, France; The Ohio State University, Columbus, OH; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Centro Integrado de Oncologia de Curitiba, Curitiba, Brazil; Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Conventional chondrosarcoma (CS) is the most common chondrosarcoma subtype, accounting for 85% to 90% of all chondrosarcoma cases. A meta-analysis of 466 patients with CS reported the detection of IDH1/2 mutations in 51.2% of patients (38.7% IDH1 and 12.1% IDH2 mutations, mutually exclusive except for one case). In a phase 1 study (NCT02073994), the long term follow-up with a data cut-off date of 15 September 2022, showed that patients with advanced conventional CS (N = 13) who were treated with the IDH1 inhibitor ivosidenib had a median progression-free survival (PFS) of 7.4 months, a 6-month PFS rate of 53.8%, and an overall response rate (ORR) of 23.1% including 2 partial responses and 1 complete response. Ivosidenib demonstrated manageable toxicity with mostly grade 1 or 2 treatment emergent adverse events (AEs) (Tap et al. J Clin Oncol. 2023;41:11532). The current phase 3 CHONQUER study was designed to assess the efficacy and safety of ivosidenib treatment in patients with grades 1, 2 and 3 conventional CS. **Methods:** The CHONQUER study (NCT06127407) is a phase 3, international, multicenter, double-blind, randomized, placebo-controlled study of ivosidenib for patients with locally advanced or metastatic IDH1 mutant conventional CS untreated or previously treated with 1 systemic treatment regimen. Key eligibility criteria include a histopathological diagnosis of conventional CS (grades 1, 2, or 3), locally-advanced or metastatic setting not eligible for curative resection; ECOG PS 0-1; measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1); received 0 or 1 prior systemic treatment regimen in the advanced/metastatic setting for CS; radiographic progression/recurrence of disease over a period of 6 months according to RECIST v1.1 and IDH1 gene-mutated disease confirmed by central laboratory testing with the Ion Torrent Oncomine Dx Express Test. A total of 136 patients are planned to be enrolled and will be randomized 1:1 to ivosidenib or a matched placebo control. Randomization will be stratified by disease grade (grade 1 versus 2 versus 3) and locally advanced versus metastatic disease. The primary endpoint is PFS confirmed by Blinded Independent Central Review (BIRC) in grade 1 and 2 patients. The key secondary endpoints include PFS based on BIRC for all randomized patients, overall survival (OS) (both grade 1 and 2 and all randomized patients). Other secondary endpoints include PFS by investigator, overall response, duration of response, time to response, disease control, duration of disease control, adverse events, and health-related quality of life. 92 sites from 12 countries are planned to participate, including North and South America, Europe and Asian countries. Clinical trial information: NCT06127407. Research Sponsor: Servier.

TPS11583 Poster Session

Phase I/II study to evaluate the feasibility and efficacy of sequential abemaciclib and gemcitabine treatment in patients with retinoblastoma (Rb)-positive leiomyosarcoma (LMS) and dedifferentiated liposarcoma (DDLPS).

Elise F. Nassif Haddad, Khandan Keyomarsi, Heather Y. Lin, Alexander J. Lazar, Wei-Lien Wang, Charles Manning, Guofan Xu, Osama F Mawlawi, Lorraine Cheryl Pelosof, Kelly Hunt, Funda Meric-Bernstam, Neeta Somaiah; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; National Cancer Institute, Cancer Therapy Evaluation Program, Rockville, MD; Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX

Background: LMS and DDLPS are aggressive malignancies with limited effective therapies in the advanced setting. Approximately 50% of LMS and nearly all DDLPS retain functional Rb protein, suggesting sensitivity to cell cycle inhibition. Our preclinical studies have demonstrated that combining sequential abemaciclib, a selective CDK4/6 inhibitor that induces cell cycle arrest, followed by gemcitabine timed with synchronized cell cycle reentry, results in synergistic antitumor activity in Rb-positive sarcomas. Sequential administration of abemaciclib followed by gemcitabine enhances apoptosis, impairs DNA repair mechanisms, and induces sustained cell cycle arrest. **Methods:** This is a multicenter, open-label, phase 1/2 clinical trial conducted through the National Cancer Institute (NCI), enabling broad, nationwide patient enrollment. The phase 1 dose-escalation portion will determine the maximum tolerated dose and recommended phase 2 dose of sequential abemaciclib and gemcitabine in patients with advanced/metastatic soft-tissue sarcomas. Part A of phase 1 will use biomarkers of cell cycle (functional positron emission tomography imaging using [18]F-fluoro-3'-deoxy-3'-L-fluorothymidine and thymidine kinase activity) to determine the optimal schedule of sequencing. Part B of the phase 1 will follow the BOIN design. Eligible patients must have histologically confirmed LMS or DDLPS with Rb positivity confirmed by immunohistochemistry, measurable disease, ECOG performance status ≤2, and adequate organ function. Prior gemcitabine therapy is permitted in phase 1 but excluded in phase 2. Phase 1 Part A is restricted to MD Anderson only enrollment due to the requirements of biomarker integration and timing. In the randomized phase 2 portion, patients will be randomized 1:1 (stratified by DDLPS vs LMS) to receive either (1) sequential abemaciclib followed by gemcitabine or (2) gemcitabine and docetaxel. The primary endpoint is progression-free survival, with secondary endpoints including objective response rate, overall survival, and safety. Correlative studies will analyze tumor biopsies and blood samples collected at baseline, after two treatment cycles, and at disease progression. Biomarker analyses will include RB1 expression profiling, whole exome sequencing, RNA sequencing, and circulating tumor DNA. Clinical trial information: NCT06498648. Research Sponsor: ETCTN - CTEP.

TPS11584 Poster Session

A phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of emactuzumab in patients with tenosynovial giant cell tumor (TANGENT).

Hans Gelderblom, Emanuela Palmerini, Jean-Yves Blay, Michiel van de Sande, Javier Martin Broto, Raul Terés, Madhu Davies, Elyse Seltzer, Sander Veltkamp, Gabriel Tinoco; LUMC Leids Universitair Medisch Centrum, Leiden, Netherlands; Osteoncology, Bone and Soft Tissue Sarcomas and Innovative Therapies - IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy; Univ Lyon, Claude Bernard Lyon 1 University, INSERM 1052, CNRS 5286, Centre Léon Bérard, Cancer Research Center of Lyon, Lyon, France; Leiden University Medical Center, Leiden, Netherlands; Fundacion Jimenez Diaz University Hospital, Institute of Biomedicine of Seville, University of Seville, Seville, Spain; Hospital de Sant Pau, Barcelona, Spain; SynOx Therapeutics, Oxford, United Kingdom; SynOx Therapeutics, Philadelphia, PA; The Ohio State University, Columbus, OH

Background: Tenosynovial giant cell tumor (TGCT) is a rare, non-malignant, locally aggressive tumor of the synovium, primarily affecting knee, hip, and ankle joints. TGCT is caused by excessive production of colony stimulating factor 1 (CSF-1), a cytokine involved in the proliferation, differentiation, and survival of monocytes and macrophages. It is a chronically debilitating disease, causing pain, stiffness, loss of function in the affected joints and a decline in quality of life. The worldwide incidence in digits, localized, and diffuse TGCT is about 29, 10, and 4 per million person-years, respectively. Surgery remains the principal treatment option, at the cost of a high rate of tumor recurrence, and risk of damage to the affected joint and surrounding tissues. Systemic treatment options are limited. Emactuzumab is a novel monoclonal antibody, and potent and specific CSF-1 receptor (CSF-1R) antagonist, that causes apoptosis of M2-type macrophages in the tumor micro-environment, thereby inhibiting tumor growth. In a phase Ia/b study, emactuzumab was administered i.v. at doses varying from 900-2000 mg (cycles ranging 1-14) in advanced diffuse TGCT patients (Cassier et al, EJC, 2020). Emactuzumab was well tolerated and showed rapid and pronounced responses with an objective response rate (ORR) of 71%, which was durable with an ORR of 70% and 64% after one or two years, respectively. Clinical activity was associated with symptomatic improvement. The optimal biological dose of emactuzumab, defined as 1000 mg q2w, is under investigation in the Phase 3 trial. Emactuzumab was granted an Orphan Drug Designation by the European Medicines Agency in March 2022. **Methods:** TANGENT (NCT05417789) is a randomized, double-blind, placebo-controlled trial designed to confirm the efficacy and safety of emactuzumab in TGCT patients not amenable for surgery. The primary endpoint is efficacy, assessed as ORR at 6 months by MRI per RECIST v1.1. Key secondary endpoints include patient-reported outcomes (PROMIS-PF), range of motion, pain and stiffness, and other antitumor activity (e.g. TVS). In Part 1, subjects will be randomized 2:1 to receive either emactuzumab 1000 mg or placebo i.v. q2w for 5 doses over 10 weeks, followed by an observation period of 3 months. Part 2 is a follow-up phase from 6-24 months post randomization during which subjects whose TGCT worsens may be eligible for emactuzumab. The study is actively recruiting. Assessments include tumor evaluation, physical examination, vital signs, electrocardiograms, questionnaires, urinalyses, and blood tests for hematology, biochemistry, and PK of emactuzumab. Safety will be assessed by laboratory assessments and evaluation of adverse events. Clinical trial information: NCT05417789. Research Sponsor: SynOx Therapeutics.

TPS11585 Poster Session

ETCTN 10563: A phase I study of peposertib and liposomal doxorubicin for advanced or metastatic leiomyosarcoma and other sarcomas.

Candace L. Haddox, Karla V. Ballman, Elise F. Nassif Haddad, Scott Michael Schuetze, Melissa Amber Burgess, Alice P. Chen, Ludimila Cavalcante, Emily E. Jonczak, Brian Andrew Van Tine, Steven Gore, Jonathan Fletcher, Suzanne George; Dana-Farber Cancer Institute, Boston, MA; Mayo Clinic, Rochester, MN; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Michigan, Ann Arbor, MI; Division of Hematology Oncology, UPMC Hillman Cancer Center/University of Pittsburgh, Pittsburgh, PA; Developmental Therapeutics Clinic, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD; Emily Couric Clinical Cancer Center, University of Virginia, Atlanta, GA; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Washington University in St. Louis, St. Louis, MO; Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD; Harvard Medical School, Boston, MA

Background: Soft tissue sarcomas (STS) with genomic complexity are often aggressive but may be sensitive to further genotoxic stress. Leiomyosarcoma (LMS), a common STS, frequently harbors genomic complexity and DNA damage response (DDR) dysregulation. Preclinical data showed hyper-dependency on DNA-PK-mediated non-homologous end joining (NHEJ) DDR, and low-dose liposomal doxorubicin (LD-LPD) synergized with the DNA-PK inhibitor peposertib to inhibit tumor growth in LMS models. We hypothesize that a low, sensitizing dose of LPD enhances DNA damage and safely synergizes with peposertib in LMS and other genomically complex STS. **Methods:** This phase 1, open label, multicenter dose escalation and dose expansion study (NCT05711615) evaluates LD-LPD given intravenously (IV) on day 1 of 28-day cycles with peposertib given orally (PO) twice daily (BID) continuously (Table). Up to 18 patients (pts) over 18 years-old with advanced or unresectable LMS, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, and synovial sarcoma, ECOG performance status ≤2, who received ≥1 prior line of systemic therapy (including anthracycline ≤300 mg/m^2) are eligible for dose escalation. Dose expansion will include 12 pts with LMS. The primary objective is to determine the recommended phase 2 dose of LPD+peposertib based on the dose limiting toxicity rate. The Bayesian Optimal Interval (BOIN) design will inform dose escalation decisions. Secondary endpoints for the expansion cohort include adverse event rate, progression-free survival, and objective response rate per RECIST v1.1. Potential predictive biomarkers and changes in DDR biomarkers will be evaluated on biopsies during screening and at cycle 1 day 7. Circulating tumor DNA (ctDNA) collected at baseline (dose escalation and dose expansion), on treatment and at progression (dose expansion) will be correlated with disease activity and response. This trial activated on 8-May-2023 through the Experimental Therapeutics Clinical Trials Network (ETCTN) and is enrolling at select sites in the United States. Dose escalation is ongoing as of January 2025. Clinical trial information: NCT05711615. Research Sponsor: National Institutes of Health/National Cancer Institute (NIH/NCI); National Cancer Institute/U.S. National Institutes of Health; Merck KGaA, Darmstadt, Germany CrossRef Funder ID: 10.13039/100009945.

Planned dose levels for dose escalation.

Dose Escalation Schedule

	Dose	
Dose Level	**Liposomal doxorubicin**	**Peposertib (tablet)**
-1	10 mg/m^2 IV	50 mg PO BID
0*	10 mg/m^2 IV	100 mg PO BID
+1	10 mg/m^2 IV	150 mg PO BID
+2	10 mg/m^2 IV	200 mg PO BID
+3	15 mg/m^2 IV	200 mg PO BID
+4	20 mg/m^2 IV	200 mg PO BID

*Starting dose.

TPS11586 **Poster Session**

The phase II study of pembrolizumab plus lenvatinib for patients with unresectable cutaneous angiosarcoma (Pembro-Lenva for cAS/PLAS trial).

Dai Ogata, Eiji Nakano, Takeru Funakoshi, Akira Takahashi, Jun Asai, Motoki Nakamura, Kenjiro Namikawa, Ryunosuke Machida, Masayuki Yokoyama, Haruhiko Fukuda, Yukari Nagasaka, Kazumi Kurishita, Yoshie Shuda, Kenta Anjo, Kanako Kondo, Masako Inaba, Satoshi Kawashima, Takako Hitomi, Natsuko Tsuda Okita, Naoya Yamazaki; National Cancer Center Hospital, Tokyo, Japan; Department of Dermatology, Keio University School of Medicine, Tokyo, Tokyo, Japan; Department of Dermatologic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Dermatology Kyoto Prefectural University of Medicine, Kyoto, Japan; Nagoya City University, Nagoya, Japan; Clinical Research Support Office, National Cancer Center Hospital, Tokyo, Japan; Data Management Section, Data Management Division, Clinical Research Support Office, National Cancer Center Hospital, Tokyo, Japan; Clinical Trial Management Section, Research Management Division, Clinical Research Support Office, National Cancer Center Hospital, Tokyo, Japan

Background: Cutaneous angiosarcoma (cAS) is a rare cancer that often occurs in elderly people with common recurrence and metastasis after surgery. Chemotherapy, radiation therapy, and their combination are widely used, but their effectiveness is insufficient. With the increasing number of cAS patients due to the aging population, the development of effective treatment is urgently required. Previously, it has been reported that cancer shrank in 18% (5 out of 27) of patients after 2 months of paclitaxel administration in a clinical trial. Therefore, paclitaxel has become more commonly used for cAS. Other options include anthracycline anticancer drugs and gemcitabine. However, even with these anticancer drugs (and radiation therapy), cAS progresses quickly, and some reports have said that the 5-year survival rate is 9%. This study is planned to develop safer and more effective treatment for cAS. Pembrolizumab is an immune checkpoint inhibitor with PD-1 receptor-ligand interaction and lenvatinib is a multikinase inhibitor that inhibits tumor angiogenesis. The combination is expected to have strong therapeutic efficacy due to the immunomodulatory effects of pembrolizumab and the inhibitory effects of lenvatinib. **Methods:** This investigator-initiated, prospective, multicenter, non-randomized phase II trial evaluates the efficacy and safety of pembrolizumab plus lenvatinib for patients with unresectable cAS. Eligible patients are aged ≥18 years (≤85 years), histologically diagnosed with cAS, and both untreated and previously treated patients. The primary endpoint of this study is to confirm the response rate of pembrolizumab plus lenvatinib combination therapy for unresectable cAS based on RECST 1.1 at central review. The secondary endpoints are response rate (primary investigator assessment), progression-free survival, overall survival, disease control rate, duration of response, time to response, incidence of adverse events (AEs), incidence of drug-related adverse events (adverse drug reactions, ADRs), and incidence of serious AEs/ADRs. We estimated a threshold response rate of 18% and an expected response rate of 35%. The planned sample size is 38 patients (25 untreated patients and 13 treated) to provide a power of 70% with one-sided alpha of 5%. The planned accrual period is 2 years, and the follow-up period is 2 years; interim analysis will be performed at the enrollment of 20 patients is completed. The trial began in February 2025. Clinical trial information: NCT06673628. Research Sponsor: None.

TPS11587 Poster Session

Integrating early palliative care in advanced sarcoma patients for enhanced quality of life: The SARQUALITY study.

Catherine S. Weadick, Natalie Pulenzas, Harleen Toor, Victor Cellarius, Haydée Williams Sanchez, Jasjeet Kaur Matharu, Abdulazeez Salawu, Geoffrey Alan Watson, Abha A. Gupta, Erica C. Koch Hein, Albiruni Ryan Abdul Razak; Princess Margaret Cancer Centre, Toronto, ON, Canada; Division of Palliative Care, Mount Sinai Hospital, Toronto, ON, Canada; Division of Medical Oncology, Mount Sinai Hospital, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Division of Medical Oncology, Mount Sinai Hospital, Sinai Health, University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre – University Health Network, University of Toronto, Toronto, ON, Canada; Pontificia Universidad Católica de Chile, Santiago, Chile; Mount Sinai Hospital, Toronto, ON, Canada

Background: Patients with advanced cancer may experience physical and psychological symptoms impacting health-related (HRQOL). The World Health Organization defined palliative care as "an approach that improves the quality of life of patients and their families" by identification and management of pain and other symptoms, spiritual and psychosocial assessments and interventions, facilitation of home and community-based supports, and transition to end-of-life care. Early palliative care (EPC) integration with cancer-directed treatment can enhance patient-reported outcomes (PROs). However, patients with sarcoma have been underrepresented in these studies, underscoring the need to evaluate the role and benefits of EPC in this population. This study aims to determine whether EPC alongside standard oncological care (SOC) improves PROs for patients with advanced sarcoma compared to usual care. **Methods:** This is a single program, dual institution phase 2 open-label clinical trial designed to assess whether EPC improves the HRQoL of patients with advanced sarcoma. Main eligibility criteria at enrolment include systemic treatment naïve patients over the age of 18 years with histologically proven advanced sarcoma, ECOG 0-2, English speaking and life expectancy of over 6 months. Enrolled patients are randomized 1:1 to either SOC alone or with EPC. Patients randomized to EPC will be reviewed by palliative care within 2 weeks of randomization. EPC will include routine in person (or virtual) contact integrated into their oncology visits and access to a 24-hour on-call service. Patients receiving SOC alone will be referred to palliative care upon emergence of uncontrollable symptoms or upon request by the patient. Patients on both arms will receive standard of care follow-up with their oncology teams and complete Edmonton Symptom Assessment System (ESAS) and EORTC QLQ-C30 questionnaires at baseline, weeks 6, 12 and 24. For the primary endpoint, EPC will be considered effective if ESAS score decreases at week 12 compared to baseline using T test, with one-sided significance level set to be 0.05. The secondary endpoints include EORTC QLQ-C30 score change (baseline to weeks 6, 12 and 24), number of extra clinic visits, emergency department attendance and overall survival at 6 and 12 months. Comparison between the two arms, assessing both scores, will be done using Fisher's exact or Chi-square test. Generalized linear mixed model will be carried out to examine the difference between the arms over time. To ensure this trial is powered to determine a significant statistical difference, we plan to enroll 136 patients with an estimated accrual period up to three years. This study commenced enrolment March 2024 and to date (January 2025) 27 patients have been recruited with 13 (48%) randomized to EPC. An amendment is currently ongoing to include the use of electronic wearables as part of the study evaluation. Research Sponsor: None.

TPS11588 Poster Session

A multicenter, randomized, global phase 3 study to assess the efficacy and safety of intratumoral (IT) INT230-6 (SHAO, vinblastine, cisplatin) as monotherapy compared with standard of care systemic chemotherapy in adults with locally recurrent, inoperable, or metastatic soft tissue sarcomas (STS; INVINCIBLE-3).

Sant P. Chawla, Abdul Razak, James S. Hu, Arun S. Singh, Kirsten Leu, David A. Liebner, Margaret von Mehren, Daniel Pink, Raul Terés, Claudia Valverde, Richard F. Riedel, Kim Guedes, Brian Schwartz, Erlinda Maria Gordon, Lewis H. Bender, Christian Meyer; Sarcoma Oncology Center, Santa Monica, CA; University Health Network, Toronto, ON, Canada; Division of Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; University of California, Los Angeles Translational Oncology Research, Santa Monica, CA; Nebraska Cancer Specialists, Omaha, NE; The Ohio State University Wexner Medical Center, Columbus, OH; Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA; Helios Klinikum Bad Saarow-Sarcoma Center Berlin-Brandenburg, Bad Saarow, Germany; Santa Creu i Sant Pau, Barcelona, Spain; Vall d'Hebron University Hospital, Barcelona, Spain; Duke Cancer Institute, Durham, NC; Intensity Therapeutics, Westport, CT; Intensity Therapeutics, Inc., Westport, CT; Johns Hopkins Hospital, Baltimore, MD

Background: Soft tissue sarcomas (STS) are a rare and diverse set of tumors. Systemic chemotherapy provides limited benefit for metastatic disease. INT230-6 is a novel formulation of cisplatin (CIS) and vinblastine (VIN) with a tissue dispersion enhancer (SHAO). The drug's unique chemistry permits dispersion throughout tumors and diffusion into the cancer cells after IT injections. The drug causes apoptosis and recruits T-cells to the tumor. An open-label, phase 1/2 study was completed with locally advanced, unresectable, or metastatic adult patients with 11 STS subtypes. Patients had a median of 3 prior lines. Biopsied tissue from pre- and post-dosed tumors[2] showed immune engagement post-dose. PK data showed that >95% of VIN stayed in the tumor. There were no dose-limiting toxicities up to 175 mL (87.5 mg CIS, 17.5 mg VIN). The disease control rate was 93%. Uninjected tumors shrank. The median OS for INT230-6 alone (n=15) was 21.3 CI (4.7, NR) months. The maximum severity of INT230-6 treatment-related adverse events (TRAEs) in STS patients was 6.7% grade 1, 60% grade 2, and 33% grade 3 (no related grade 4 or 5 AEs). The most common TRAEs were pain, fatigue, and nausea. **Methods:** IT-03 is a 2:1 randomized trial comparing INT230-6 as monotherapy to an investigator's choice of pazopanib, trabectedin, or eribulin, per label. A total of 333 patients in 2L/3L will be enrolled in the US, Canada, Europe, and Australia. INT230-6 dose is set by tumor size. INT230-6 is given IT Q2W for up to 5 doses to as many tumors >1 cm as is deemed safe. Maintenance is Q12 weeks for up to 22 months. Statistics: 90% power to detect a survival HR of 0.65 with 3 interim assessments at 20%, 40%, and 60% of participants events (deaths). The final analysis is at 80% of events. There is a two-sided total alpha = 0.05, allocated as follows: interim #1 = 0.0039; #2 = 0.0184; final = 0.043. Includes up to 60 sites: several sites are now recruiting. Inclusion criteria: Must be ≥ 18 yo, and provide written consent, Proven, unresectable, locally advanced, or metastatic STS; Must have received at least one line of therapy and progressed after anthracycline therapy. 1 tumor for injection of at least 2 cm. Adequate organ function in screening; lab values of: Neutrophils ≥ 1500/μL (≥ 1.5× 10^9/L). PT, and INR ≤ 1.5× ULN, platelets ≥ 100,000/μL; hemoglobin ≥ 9 g/dL. Criteria must be met without erythropoietin dependency or packed red blood cell transfusion within last 2 weeks. Creatinine normal; or clearance > 50 mL/min by the C-G equation. ALT SGOT/ AST SGPT ≤ 2.5× ULN without, and ≤ 5× ULN with hepatic metastases. Bilirubin (BR) ≤ 1.5× ULN (except those with Gilbert's syndrome, who must have total BR ≤ 3.0 mg/dL [< 52 μmol/L]). CPK ≤ 2.5× ULN. Clinical trial information: NCT06263231. Research Sponsor: Intensity Therapeutics.

TPS11589 Poster Session

Trial in progress: TAGGED—A phase 2 study using low dose/metronomic trabectedin, gemcitabine, and dacarbazine as 2nd/3rd/4th line therapy for advanced soft tissue sarcoma (NCT04535271).

Samantha Jeffrey, Jason Ballon, Anmol Dia Agarwal, Lauren Woolsey, Princess "Angela" Savage, Vanessa Xayasak, Sarosh Syed, Victoria S. Chua-Alcala, Ania M Moradkhani, Doris V. Quon, Steve Wong, Neal Shiv Chawla, Erlinda Maria Gordon, Sant P. Chawla; Sarcoma Oncology Center, Santa Monica, CA

Background: Despite significant progress in the field of cancer medicine, the prognosis of advanced soft tissue sarcoma (STS) patients remains poor. Standard of care includes surgery for resectable tumors, generally paired with adjuvant radiation and chemotherapy. Anti-neoplastic drugs trabectedin, gemcitabine, and dacarbazine, have all demonstrated efficacy in STS. However, standard doses often result in toxicity and chemoresistance. Thus, we hypothesize that a low dose/metronomic combination regimen of intravenous trabectedin, gemcitabine, and dacarbazine will produce synergistic/additive activities without additive toxicities, providing a safer and more efficacious alternative to standard chemotherapy regimens. **Methods:** This Phase 2 open-label single-site study (NCT04535271) will evaluate the efficacy and safety of low dose/metronomic trabectedin, gemcitabine, and dacarbazine in prolonging progression free survival in patients with advanced STS. A total of 80 previously treated patients, 18 years or older, with locally advanced, unresectable or metastatic STS will receive trabectedin 0.5mg/m2 CIV over 24 hours, gemcitabine 200 mg/m2 IV, and dacarbazine 200 mg/m2 IV on D1 and D8. Each cycle will be 3 weeks. Treatment will continue up to one year or until disease progression or unacceptable toxicity. The primary endpoint is Progression Free Survival (PFS), estimated by the Kaplan-Meier method with two-sided 95% confidence interval. Secondary endpoints include best overall response (BOR) and duration of response (DOR) by RECIST v1.1 criteria, PFS rate, overall survival (OS) rate at 4, 6, and 12 months, and incidence of treatment-related adverse events (TRAEs). The Intention-To-Treat (ITT) population, consisting of all patients who received at least one dose of each study drug, will be used for adverse event analysis. The Modified Intention-To-Treat (MITT) population, consisting of patients who completed the first 2 cycles and have had follow-up imaging, will be used for analysis of PFS, BOR, DOR, PFS, and OS. Key inclusion criteria include a pathologic diagnosis of locally advanced or metastatic STS, previously treated patients with measurable disease by RECIST v1.1, ECOG $\leq$ 2, life expectancy of at least 3 months, acceptable liver and renal function, and acceptable hematological and organ functions. Key exclusion criteria include patients who have progressed with all three study drugs, known hypersensitivity to any of the three study drugs, currently receiving treatment or are $<$14 days since ending treatment with another investigational device or drug study, pregnant or breastfeeding or who have plans to become pregnant, breastfeed, or unwilling to use female or male contraception. The study has enrolled 13 of 80 patients and is actively recruiting. Clinical trial information: NCT04535271. Research Sponsor: None.