11500 Oral Abstract Session

Efficacy, safety, and patient-reported outcomes of vimseltinib in patients with tenosynovial giant cell tumor: Results from the phase 3 MOTION trial.

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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. TGCT requires a therapy with low toxicity as patients (pts) may need long-term treatment; there is an unmet need for an effective, well-tolerated CSF1 receptor (CSF1R)-targeted therapy that improves functional health and quality of life (QoL). Vimseltinib is an investigational, oral, switch-control tyrosine kinase inhibitor specifically designed to selectively and potently inhibit CSF1R. Here we report results from the MOTION trial. **Methods:** MOTION is a global, phase 3, double-blind study of vimseltinib in pts with symptomatic TGCT not amenable to surgery (NCT05059262). Randomization was 2:1 to vimseltinib 30 mg twice weekly or matching placebo (pbo) for 24 weeks. The primary endpoint was objective response rate (ORR) assessed by blinded independent radiological review (IRR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) at week 25. Key secondary endpoints assessed at week 25 were ORR by IRR per tumor volume score (TVS), change from baseline in active range of motion (ROM) of the affected joint and patient-reported outcomes (PROs; PRO Measurement Information System physical function score [PROMIS-PF], worst stiffness numeric rating scale, and EuroQol Visual Analog Scale [EQ-VAS]), and brief pain inventory worst pain response. Safety was also evaluated. Data cutoff was August 22, 2023. **Results:** Overall, 123 pts were randomized to vimseltinib (n = 83) or pbo (n = 40). Median age was 44 years, 59% of pts were female, and the most common primary disease location was the knee (67%). ORR at week 25 by IRR per RECIST v1.1 and per TVS were significantly higher for vimseltinib vs pbo (RECIST: 40% vs 0%, $P < 0.0001$; TVS: 67% vs 0%; $P < 0.0001$). Significant improvements from baseline to week 25 were observed with vimseltinib vs pbo in active ROM (18.4% vs 3.8%; $P = 0.0077$), physical function (PROMIS-PF: 3.3-point difference between arms, $P = 0.0007$), worst stiffness (−1.8-point difference, $P < 0.0001$), and health status (EQ-VAS: 7.4-point difference, $P = 0.0155$). There were also significantly more pain responders treated with vimseltinib (48% vs 23%; $P = 0.0056$). Most non-laboratory treatment-emergent adverse events were grade 1/2, and there was no evidence of cholestatic hepatotoxicity or drug-induced liver injury. **Conclusions:** Patients treated with vimseltinib experienced statistically significant and clinically meaningful improvements in ORR by RECIST v1.1 and by TVS, active ROM, physical function, stiffness, health status, and pain vs pbo. Vimseltinib is an effective, well-tolerated CSF1R-targeted therapy that demonstrates significant clinical benefit and improves functional health and QoL in pts with symptomatic TGCT not amenable to surgery. Clinical trial information: NCT05059262. Research Sponsor: Deciphera Pharmaceuticals, LLC.

11501 Oral Abstract Session

StrateGIST 1: A first-in-human (FIH), phase 1 study of IDRX-42 in patients with metastatic gastrointestinal stromal tumors resistant to prior treatment with tyrosine kinase inhibitors (TKIs).

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Background: Resistance to kinase inhibitors in gastrointestinal stromal tumors (GIST) is mainly driven by secondary mutations in *KIT*, and currently available TKIs fail to inhibit the full spectrum of secondary *KIT* mutations.IDRX-42 is an oral, potent, and highly selective inhibitor of the KITtyrosine kinase, active against multiple primary and secondary resistance mutations in KIT-driven GIST. We present data from the ongoing FIH phase (ph) 1 study evaluating IDRX-42 in patients (pts) with metastatic GIST in 2nd or later lines of therapy after failure of imatinib and other drugs. **Methods:** This ph 1 study evaluates the safety, tolerability, pharmacokinetics, and antitumor activity of oral IDRX-42 in adult pts with *KIT*-mutant GIST in dose escalation (ph1a) and defines the recommended dose for continued development (ph 1b). Ph 1b comprises 4 cohorts including pts without prior exposure to TKIs (1st line), pts treated with prior imatinib only (2nd line) and later line treatment cohorts. Correlative studies include sequential circulating tumor DNA (ctDNA) analyses and metabolic imaging using 18FDG-PET. **Results:** As of January 2, 2024, 42 pts received IDRX-42 in the ph 1a portion of the study with median treatment duration of 19+ (range 2-73+) weeks, with 30 pts remaining on treatment as of data cutoff. The median number of prior TKI therapy lines was 4 (range 1-6). Primary driver mutations were in *KIT* exon (ex) 11 (n = 27), ex 9 (n = 13) and ex 8 (n = 2). To date, five dose levels (120, 240, 400 and 600 mg QD; 400 mg BID) have been deemed safe to continue escalation. MTD has not been reached. A total of 39/42 pts are evaluable for efficacy; 9 achieved objective partial response (PR) per mRECIST (5 confirmed, 4 pending) across all doses studied. Three of 6 patients receiving IDRX-42 as 2nd line therapy have confirmed PRs at 120 mg QD, 400 mg QD, and 400 mg BID respectively. The clinical benefit rate (mRECIST PR or stable disease ≥16 weeks) is 71% overall and 100% in 2nd line. Sequential analyses of ctDNA show reductions across all primary and secondary *KIT*mutations. Treatment-related adverse events (TRAE, CTCAE v5.0) were mainly low grade. The most frequently reported TRAE (≥25%) were gastrointestinal symptoms (diarrhea, nausea, vomiting, decreased appetite, dysgeusia) and fatigue. Eight of 42 pts reported Grade 3/4 TRAEs including gastrointestinal symptoms, fatigue and anemia. Two events qualified as DLT, 1 at 600 mg QD (syncope) and 1 at 400 mg BID (vomiting); after dose reduction both pts continued IDRX-42 for more than 8 and 5 months, respectively. Only two patients discontinued treatment due to TRAEs. **Conclusions:** IDRX-42 demonstrates promising clinical activity and a favorable safety profile in patients with advanced GIST following resistance to prior TKIs. Dose finding continues, and additional cohorts are ongoing. Clinical trial information: NCT05489237. Research Sponsor: IDRx, Inc.

11502 Oral Abstract Session

Updated efficacy results of olverembatinib (HQP1351) in patients with tyrosine kinase inhibitor (TKI)-resistant succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors (GIST) and paraganglioma.

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Background: SDH-deficient GIST is a rare type of GIST, mainly observed in the stomach of children and adolescents or young adults < 30 years of age. No active targeted therapies have been identified in this subset of GIST. Olverembatinib, approved in China for treatment of patients with chronic myeloid leukemia, has shown promising clinical efficacy in SDH-deficient GIST. We report here updated efficacy data in SDH-deficient GIST and preliminary efficacy data in paraganglioma, which is an SDH-deficient–related tumor. **Methods:** The aim of this study was to evaluate the safety and efficacy (per RECIST v1.1) of olverembatinib in patients with TKI-resistant SDH-deficient GIST and other solid tumors. Olverembatinib was administered orally once every other day (QOD) in 28-day cycles. **Results:** As of December 27, 2023, 26 patients with SDH-deficient GIST (confirmed by IHC) had received ≥ 1 dose of olverembatinib (median [range] age, 30 [13-56] years), and 25 had received 1 to 4 TKIs (42.3% of patients, ≥ 3; Table 1). Olverembatinib was administered QOD in doses ranging from 30 to 50 mg (30 mg [n = 6]; 40 mg [n = 14]; 50 mg [n = 6]). The median (range) treatment duration was 15.6 (1.8-42.3) months. A total of 6 of 26patients experienced partial response (PR) as the best response. A further 18 patients had stable disease (SD) lasting > 4 cycles. The clinical benefit rate (CBR; complete response [CR] + PR + SD > 4 cycles) was hence 92.3% (24/26) and the longest treatment duration was 40 months. After a median follow-up of 17.0 (4.1-57.5) months, the median progression-free survival (PFS) was 25.7 months (12.1-not reached [NR]). Among the 6 patients with paraganglioma enrolled in this study, best responses were observed in 5, with SD lasting > 4 cycles (CBR, 83.3%), and the median PFS was 8.25 (1.87-NR) months. The adverse event profile was the same as previously reported (Qiu H et al, *J Clin Oncol* 41:11540), with no newly emergent safety issues observed. **Conclusions:** Olverembatinib was well tolerated. The CBR exceeded 90%, and the estimated median PFS was significantly prolonged, indicating potential benefit of this treatment and providing a benchmark for future studies in this rare subtype of GIST. Clinical trial registration: NCT03594422; internal study identifier: SJ-0003. Clinical trial information: NCT03594422. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

Characteristics	N = 26
Median age (range), yr	30 (13-56)
Female, no. (%)	19 (73.1)
Primary tumor site, no. (%)	
Stomach	26 (100)
Prior TKIs, no. (%)*	
0	1 (3.8)
1	9 (34.6)
2	5 (19.2)
≥ 3	11 (42.3)

*Percentages do not sum to 100 because of rounding.

11503 Oral Abstract Session

Final results of a randomized phase II/III study comparing perioperative adriamycin plus ifosfamide and gemcitabine plus docetaxel for high-grade soft tissue sarcomas: Japan Clinical Oncology Group study JCOG1306.

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Background: We have previously reported long-term follow-up results of the favorable efficacy of perioperative chemotherapy with adriamycin plus ifosfamide (AI) for high-grade soft tissue sarcomas (STS) (JCOG0304). We have also reported the results of the second interim analysis of a phase II/III trial to confirm the non-inferiority of perioperative gemcitabine plus docetaxel (GD) to AI for high-grade STS (JCOG1306) in 2020 ASCO Annual Meeting. This study was terminated at the preplanned second interim analysis based on the point estimate of hazard ratio (HR) being above the pre-specified allowable HR of 1.61. The estimated 2-year overall survival (OS) was 94.3% (95% confidence interval (CI) 83.4–98.1%) in AI and 91.6% (80.9–96.4%) in GD (HR 2.55, 95% CI 0.80–8.14) in the analysis. We herein report the final results of JCOG1306 at 5-year follow-up. **Methods:** Patients with operable, FNCLCC grade 2/3 STS primary tumor (T2bN0M0 or anyTN1M0, AJCC 7th edition) or first local recurrent tumor in the extremities or trunk were randomized to AI or GD. Chemotherapy consisted of adriamycin 60 mg/m^2 plus ifosfamide 10 g/m^2 for AI or gemcitabine 1,800 mg/m^2 plus docetaxel 70 mg/m^2 for GD. The treatments were repeated for 3 courses preoperatively and 2 courses postoperatively in a 3-week interval. The primary endpoint in phase III part was OS. Planned sample size was 140 with a one-sided alpha of 0.1, power of 0.7 and a non-inferiority margin of 8% at 3-year OS (HR of 1.61), assuming 3-year OS of AI to be 85% and that of GD as 87%. **Results:** A total of 143 patients were enrolled between February 2014 and September 2018, and 5-year follow-up has finished in September 2023. Seventy and 73 patients were assigned to AI and GD, respectively, and included in the efficacy analysis. At the final analysis with a median follow-up of 6.0 years, the estimated 5-year OS was 90.0% (95% CI 80.1–95.1%) in AI and 76.1% (64.5–84.4%) in GD (HR 2.67, 95% CI 1.23–5.80). The estimated 5-year progression-free survival was 65.2% (95% CI: 52.7–75.2%) in AI and 57.4% (45.2–67.8%) in GD (HR: 1.33, 95% CI 0.81–2.18). At the 5-year follow-up analysis, there were no treatment-related deaths in both arms. **Conclusions:** The results of the second interim analysis were confirmed in the final analysis after five-year follow-up, i.e., non-inferiority of GD to AI in terms of OS could not be confirmed. In the perioperative chemotherapy for high-grade STS in the extremities and trunk, AI remains the standard regimen. Clinical trial information: jRCTs031180003. Research Sponsor: AMED; National Cancer Center Research and Development Fund.

11504 Oral Abstract Session

SU2C-SARC032: A randomized trial of neoadjuvant RT and surgery with or without pembrolizumab for soft tissue sarcoma.

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Background: Surgery & radiation therapy (RT) yield high local control rates for soft tissue sarcoma (STS) of the extremity and limb girdle. However, patients (pts) with high-grade stage III STS are at significant risk for developing metastasis. Median survival for pts with metastatic STS is < 2 years. SARC028 (NCT02301039) evaluated the efficacy of pembrolizumab (pembro) for metastatic STS, showing 20% and 8.7% response rates in undifferentiated pleomorphic sarcoma (UPS) and pleomorphic/dedifferentiated liposarcoma (LPS), respectively. We hypothesized that neoadjuvant pembro with concurrent RT followed by surgery and adjuvant pembro for stage III UPS, including myxofibrosarcoma, or LPS would stimulate an anti-tumor immune response to eliminate micrometastatic disease & improve disease-free survival (DFS). SU2C-SARC032 (NCT03092323) is a multi-institutional, international, randomized phase 2 trial evaluating the safety and efficacy of adding pembro to standard of care (SOC) RT & surgery for pts with stage III UPS or LPS. **Methods:** Pts aged > 12 yo with stage III (FNCLCC grade 2 or 3) UPS or LPS of the extremity and limb girdle were enrolled. Pts were randomized (1:1, stratified by grade) to neoadjuvant RT (50 Gy/25 fx) then surgery (SOC arm) or neoadjuvant pembro and RT then surgery & adjuvant pembro (EXP arm). Pembro was given 200 mg IV Q3 wk for 3 doses (before, during & after RT) & up to 14 adjuvant cycles. The primary endpoint was 2-yr DFS. Secondary endpoints included local recurrence-free survival (LRFS), distant disease-free survival (DDFS), & overall survival (OS). Target enrollment of 126 evaluable patients (max 144 total) provided 80% power (1-sided $\alpha = 0.05$) to distinguish between a null hypothesis of 50% 2-yr DFS rate & alternative hypothesis of 75% 2-yr DFS rate by log-rank test, with initial analysis at 45 DFS events. Cox models were stratified by grade; primary analysis was a one-sided stratified log-rank test. **Results:** Between July 2017-November 2023, 143 patients were enrolled, predominantly with UPS (85%) & grade 3 (64%) histology. Median follow-up for alive patients is 24.1 mo. DFS in the EXP arm is significantly higher than the SOC arm ($p = 0.023$; HR 0.57, 90% CI: 0.35, 0.91). Estimated 2-yr DFS is 53% (90% CI: 43, 66%) for SOC vs 70% (90% CI: 61, 81%) for EXP arm. Currently, there is no statistically significant difference in LRFS (HR 0.55, 95% CI: 0.21, 1.42), DDFS (HR 0.57, 95% CI: 0.32, 1.01), or OS (HR 0.39, 95% CI: 0.14, 1.12). Pts with grade 3 sarcomas had improved DFS with pembro (HR 0.47, 95% CI: 0.25, 0.89), but no difference in DFS was observed in grade 2 tumors (HR 1.21, 95% CI: 0.35, 4.18). The proportion of patients with grade 3+ adverse events was significantly higher in EXP (52%) vs SOC arm (26%) ($p = 0.002$). **Conclusions:** Theaddition of neoadjuvant & adjuvant pembro to RT and surgery significantly improves DFS for pts with stage III UPS and LPS of the extremity and limb girdle. Clinical trial information: NCT03092323. Research Sponsor: SU2C; SU2C-AACR-CT02-16; Merck.

11505 Oral Abstract Session

Sintilimab, doxorubicin and ifosfamide (AI) as first-line treatment in patients with advanced undifferentiated pleomorphic sarcoma (UPS), synovial sarcoma (SS), myxoid liposarcoma (MLPS) and de-differentiated liposarcoma (DDLPS): A single-arm phase 2 trial.

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Background: Anti-PD-1 antibody had showed encouraging activity as salvage treatment in patients with certain subtypes of advanced soft tissue sarcoma. However, its role in first-line setting is uncertain. We assessed the safety and activity of sintilimab, an anti-PD-1 antibody, combined with doxorubicin (ADM) and ifosfamide (IFO) in patients with advanced undifferentiated pleomorphic sarcoma (UPS), synovial sarcoma (SS), myxoid liposarcoma (MLPS) and de-differentiated liposarcoma (DDLPS). **Methods:** This is a single-arm, phase 2 study. Systemic treatment naïve patients with metastatic or unresectable locally advanced UPS, SS, MLPS and DDLPS were treated with sintilimab (200mg, d1), ADM (60mg/m^2, d1) and IFO (1.8 g/m^2/d, d1-5) every 3 weeks for up to 6 cycles, followed by sintilimab maintenance until disease progression, unacceptable toxicities or up to 2 years. The primary endpoint was objective response rate (ORR, per RECIST 1.1), and secondary endpoints included progression free survival (PFS), overall survival (OS) and safety. **Results:** Between June 2020 and June 2023, 46 eligible patients were enrolled. 31 were male, and the median age was 47 years old. Of the 41 evaluable pts, ORR was 68.3% (28/41), including 7/8 (87.5%) UPS, 13/20 (65.0%) SS, 3/3 (100%) MLPS and 5/10 (50%) DDLPS patients. At a median follow-up time of 28.0 months (95% CI: 9.4-46.7 months), the median PFS and OS were 9.0 months (95% CI: 6.5-11.5 months) and 19.9 months (95% CI: 14.9-24.9 months), respectively. 1 DLT was observed in the first six patients during the DLT observation window. The most frequent ≥ grade 3 adverse events were leucopenia (50.0%), neutropenia (45.7%), thrombocytopenia (21.7%), anemia (21.7%), and febrile neutropenia (21.7%). **Conclusions:** The primary endpoint of ORR was met. This study indicated promising efficacy and safety of sintilimab combined with AI in the first-line treatment of UPS, SS, MLPS and DDLPS. Clinical trial information: NCT04356872. Research Sponsor: None.

11506 Oral Abstract Session

ImmunoSarc II master trial (phase II of sunitinib and nivolumab): Results from the dedifferentiated chondrosarcoma (DDCS) cohort—A GEIS, ISG and UCL study.

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Background: Dedifferentiated chondrosarcoma (DDCS) is a rare aggressive CS subtype with a dismal prognosis and no standard of care systemic therapy. For those with advanced, metastatic disease, retrospective chemotherapy studies demonstrate short-term median progression-free survival (PFS) of around 3 to 5.5 months. Benefit from checkpoint and tyrosine kinase inhibitors has been reported, however clinical trial data is scarce, and endpoints are not well defined, thus benchmarking outcomes is challenging. The IMMUNOSARC I master-trial exploring sunitinib plus nivolumab in multiple sarcoma subtypes, detected potential activity in DDCS leading to a specific cohort within the phase II trial IMMUNOSARC II (NCT03277924). **Methods:** Patients (pts) with ECOG 0-1, centrally confirmed and progressive, measurable DDCS were eligible and treated with sunitinib 37.5 mg/d for 14 days (induction phase), followed by 25 mg/d, in combination with nivolumab 240 mg every 2 weeks until progressive disease (PD) or intolerance. Imaging assessments were performed every 8 weeks. Main endpoint was 6-m PFSR with one-arm survival design (type I error α 0.05, power 0.90, H0 40%, H1 70%) and a Brookmeyer-Crowley like test was assumed with at least 14 of 23 pts required without progression at 6 months. **Results:** Between December 2019 and October 2023, 24 pts with a median age of 60 years (38-76) were enrolled in 7 centres. Sixteen pts (66%), were male. Pts had received a median of 1 (0-2) prior lines of therapy. In total, 23 pts were evaluable with a median follow-up of 20.1 months (95%CI: 11.6-28.6). Median PFS, according to local site assessment, was 5.6 months (95%CI: 4.5-6.7); the 6m-PFSR was 10 of 23 pts (46%); (95%CI: 23-66) and median overall survival 10.3 months (95%CI: 6.7-13.9). In 19 pts with RECIST measurable response, 5 pts (26.3%) achieved a partial response; 10 (52.6%) stable disease and 4 (21.1%) PD. End-of-treatment reasons were PD in 21 pts (87%), toxicity 1 pt (4.2%) with two pts (8.4%) ongoing. For safety population, the most relevant study drug-related G3-4 toxicities were neutropenia (20.9%), anemia (16.7%), and increased ALT (12.5%). **Conclusions:** Sunitinib and nivolumab demonstrated encouraging activity in advanced DDCS that did not meet the primary endpoint, but compares favourably with previous analyses of cytotoxic and targeted therapy. The combination is worthy of further exploration in conjunction with reaching a consensus on clinically meaningful endpoints in this challenging population. Translational studies to identify potential predictive biomarkers are ongoing. Clinical trial information: NCT03277924. Research Sponsor: BMS and Pfizer companies provided a budget for drug supply, logistics, and some operational/CRO costs; GEIS and ISG cooperative groups covered some operational/CRO costs in Spain and Italy; The Jon Moulton Charity Trust contributed to funding of UK patients; National Institute for Health Research UCLH Biomedical Research Centre (UK patients).

11507 Oral Abstract Session

ARTEMIS-002: Phase 2 study of HS-20093 in patients with relapsed or refractory osteosarcoma.

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Background: Patients (pts) with relapsed and refractory (R/R) osteosarcoma have a poor prognosis with limited therapeutic options. HS-20093 is a novel antibody-drug conjugate (ADC) targeting B7-H3, which showed preliminary anti-tumor activity in phase 1 ARTEMIS-001 study (NCT05276609). Here we report results in R/R osteosarcoma pts treated with HS-20093 from ARTEMIS-002 study (NCT05830123). **Methods:** ARTEMIS-002 trial is an open label, two-arm phase 2 trial in pts with R/R osteosarcoma or other sarcomas progressed upon standard systemic treatment. Based on the results of the phase 1 trial that the maximum tolerated dose was 12 mg/kg once every 3 weeks (Q3W) intravenous infusion, the osteosarcoma pts in the phase 2 trial were randomized to receiving HS-20093 either at 8 mg/kg or 12 mg/kg Q3W at a ratio of 1:1. The primary endpoint was objective response rate (ORR) according to RECIST1.1. B7-H3 expression was retrospectively evaluated by IHC in osteosarcoma FFPE tissue. **Results:** A total of 34 pts with R/R osteosarcoma were enrolled from June to December in 2023, receiving HS-20093 at the dose of either 8.0 mg/kg (N = 15) or 12.0 mg/kg (N = 19). Median age was 21.5 years (range: 18~65). At baseline, most pts were evaluated with clinical stage IV disease (32/34, 94.1%) and pulmonary metastasis (28/34, 82.4%). Twenty-two pts (64.7%) had received ≥3 prior lines therapy. Twenty-six pts (76.5%) had received 4 types of standard chemotherapies consisting of platinum, anthracyclines, ifosfamide and methotrexate. Treatment emergent adverse event (TEAEs) occurred in 33 pts (97.1%). The common grade 3/4 TEAEs (≥5%) were: neutropenia, leukopenia, thrombocytopenia, lymphopenia and anemia. The incidences of discontinuations, dose withhold and dose reductions were 2.9%, 11.8% and 23.5%, respectively. There was no TEAE leading to death. As of cut-off date (25 December, 2023), the median follow-up time was 4.1 months (95% CI: 1.4~5.5) among 21 response-evaluable pts (11 treated with 8 mg/kg and 10 with 12.0 mg/kg). The ORR of 12.0 mg/kg HS-20093 was 20.0%. Two confirmed partial responses were observed in pts with 12.0 mg/kg and remained on response until last follow-up, of which the longest duration of response was 4.0 months. The disease control rate was 81.8% (9/11) and 100% (10/10) in pts with 8 mg/kg and 12.0 mg/kg. The median progression-free survival of all 21 pts was not mature. B7-H3 is highly expressed in osteosarcoma with median H-score 185 (0~260). No correlation was observed between tumor response and B7-H3 expression level. The PK exposure of HS-20093 ADC, total Ab and payload increased with dose, approximately proportional to dose, with a half-life of 4 to 6 days, and no or minor accumulation after multiple doses of Q3W. **Conclusions:** The data has demonstrated that HS-20093 exhibited promising antitumor activity with acceptable toxicity in pts of heavily-pretreated R/R osteosarcoma. The enrollment of ARTEMIS-002 is continuing. Clinical trial information: NCT05830123. Research Sponsor: Hansoh Pharmaceutiacl Group Co, Ltd.

11508 Oral Abstract Session

SARC037: Phase II results of trabectedin given as a 1-hour (h) infusion in combination with low dose irinotecan in patients (pts) with relapsed/refractory Ewing sarcoma (ES).

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Background: Trabectedin(T) is a marine-derived minor groove DNA binding compound that alters transcription factor activity. Preclinical data suggests that T suppresses the oncogenic driver of ES, EWS::FLI1. This suppression requires a threshold concentration of T and is potentiated by low doses of Irinotecan(I). Preliminary clinical activity and reversal of the EWS::FLI1 transcriptome was seen in patients (pts) in the phase I portion of SARC037. Here we report the phase II results of T with I at the recommended dose in pts with relapsed/refractory ES. **Methods:** In this open-label multicenter study, T was given at 1 mg/m^2 as a 1-h infusion on day(D)1 with I at 25 mg/m^2 intravenously on D2 and D4 of a 21D cycle. Key eligibility criteria were EWS::FLI1 fusion transcript, age ≥6 years, ECOG ≤2, adequate organ function, and willing to have a research biopsy if safely accessible. The primary objective was to determine the objective response rate (ORR) assessed by RECIST v1.1. Secondary objectives were progression-free survival (PFS), duration of response (DOR), and safety. This study used a Simon two-stage design that required 4 or more responses (CR or PR) at the final analysis to establish treatment activity. **Results:** 18 pts enrolled from 12/2022-12/2023 across 6 sites, 8F/10M, median age 21y (9-43). Pts had a median of 3 (1-7) prior therapy lines, including I in 67% of pts. Of 16 pts evaluable for response at the cutoff date, 5 pts had a PR, and 2 pts had SD. Two pts have evaluations pending and two pts were removed for toxicity before the first evaluation. Median time to response was 2.6 months(m), 6-month PFS was 37.7% (95% CI 18.3%, 77.7%), and all responses were sustained at the time of data cutoff at 10.4+, 7.5+, 5.5+, 5.0+ and 4.6+ m. There were no G5 AEs. Most pts had molecular profiling, translocation testing, as well as ctDNA collection, quantitation, and analysis. A subset of pts had pre- and post-treatment biopsies for RNA sequencing and evaluation of the impact of drug exposure on the EWS::FLI1 transcriptome. **Conclusions:** T+I exhibited anti-tumor activity in heavily pretreated pts with ES and met its prespecified ORR with 5 PRs in 16 evaluable patients, all of which are ongoing at data cutoff. There were no unexpected safety signals. The combination of T given as a 1h infusion and low-dose I demonstrated meaningful clinical benefit and is worthy of further study in ES pts. Analysis of biological correlates is ongoing. Clinical trial information: NCT04067115. Research Sponsor: Janssen; U.S. National Institutes of Health.

11509 Clinical Science Symposium

Molecular characterization of patients with localized Ewing sarcoma targeting discrete prognostic groups: A report from the Children's Oncology Group.

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Background: Ewing sarcoma (EWS) is an aggressive bone and soft tissue cancer that primarily affects adolescents and young adults. All patients receive intensive therapy, yet 20% of patients with localized disease die and survivors are left with significant morbidity. Molecular biomarkers are needed to inform risk-stratified approaches to therapy. We thus evaluated gene fusions, copy number alterations (CNAs), mutations, immunohistochemistry (IHC), and relapse risk in a large cohort of patients with localized EWS. **Methods:** We carried out targeted sequencing on a combination of Formalin-Fixed Paraffin-Embedded (FFPE) and frozen tumor specimens from 351 patients with EWS previously enrolled on cooperative group trials (AEWS0031, AEWS1031). Gene fusions were identified using a combination of a targeted DNA assay and an RNA fusion panel. CNAs of chromosome 1q gain, 8 gain, 12 gain, and 16q loss were ascertained using ultra-low pass whole-genome sequencing (~0.1X coverage). Deleterious *STAG2* and *TP53*mutations were identified as part of the targeted DNA assay. Tissue was stained for STAG2 and scored as percent 0, 1+, 2+ and 3+ staining. Tumors with ≥50% 2+ or 3+ were considered as "expressed", those with ≥50% 0 or a deleterious gene alteration were considered "loss of expression", and those that fit neither criterion were "indeterminate." Cumulative incidence of relapse was used as the outcome measure to account for the competing risks of death and secondary malignant neoplasm. **Results:** 282 of 351 cases (80.3%) were found to have a canonical EWS fusion of *EWSR1-FLI1*, *EWSR1-ERG*, *EWSR1-ETV*, or *EWSR1-FEV*. 247 cases (87.6%) were evaluable for CNAs, with 20.6% of cases with 1q gain, 50.6% with 8 gain, 21.1% with 12 gain, 17.0% with 16q loss. In univariate analyses, chromosome 1q gain trended toward a higher cumulative incidence of relapse (5-year cumulative incidence of relapse 35%, 95% C.I. [23%,49%] vs. 21%, [16%,28%]; Gray's test p = 0.063). 277 cases (98.2%) were evaluable for mutations, with 5.1% of cases with *TP53* mutations and 7.6% of cases with *STAG2* mutations. In univariate analyses, *STAG2* mutation was associated with higher cumulative incidence of relapse (53%, [29%,73%] vs. 21%, [16%,26%]; $p < 0.001$). *TP53* mutation was also associated with worse outcome (43%, [17%,67%] vs. 22%, [17%,27%]; p = 0.039). 169 cases (59.9%) were evaluable for STAG2 IHC, and *STAG2*loss was associated with higher cumulative incidence of relapse (32%, [20%,45%] vs. 16%, [9.6%,25%]; p = 0.004). **Conclusions:** *TP53* mutation, *STAG2* mutation, and *STAG2* loss by IHC/ mutation are prognostic among patients with primary localized EWS. We will use these data to develop a framework for molecular risk stratification in localized EWS. Integration of these findings in future clinical trials may allow testing of biologically informed treatment modification in patients with localized EWS. Research Sponsor: None.

Prospective evaluation of pre-treatment ctDNA burden in localized osteosarcoma to identify patients with inferior outcomes: A report from the LEOPARD study.

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Background: Prior retrospective analyses demonstrated that elevated pre-treatment ctDNA was associated with poor outcomes in newly diagnosed localized osteosarcoma. The primary objective of the LEOPARD study (Liquid biopsy in Ewing sarcoma and osteosarcoma as a prognostic and response diagnostic) was to determine whether patients with detectable pre-treatment ctDNA have an inferior event-free survival (EFS) compared to patients with undetectable ctDNA. **Methods:** The LEOPARD study is a prospective multicenter ctDNA study for patients with bone sarcomas. Patients enrolled through 12 primary study sites, or provided samples after enrolling on the Children's Oncology Group Project EveryChild (ABTR18B1-Q). Eligible patients were 1-50 years of age at enrollment, had unresected, high-grade, localized, non-pelvic osteosarcoma and were to receive standard chemotherapy (primary centers only). We utilized a validated ctDNA assay, ultra-low pass whole genome sequencing (ULP-WGS), for ctDNA quantification based on tumor aneuploidy (limit of detection 3%). We compared EFS according to baseline ctDNA burden using two pre-specified cut points (detectable/undetectable [≥3%] and ~median [≥5%]. We planned 113 patients for 80% power to detect a difference in 2-year EFS of ~20% or greater for patients with detectable baseline ctDNA (2-year EFS: 68%) vs undetectable ctDNA (2-year EFS: 87%; one-sided log-rank test; α=0.05). **Results:** From 10/1/17 to 3/3/23, 138 patients with osteosarcoma met eligibility and enrolled (67 - primary study centers; 71 - ABTR18B1-Q). 133 patients had an evaluable pre-treatment ctDNA measurement. Median age was 14.2 years (range: 4.2-30.3) and 50% of patients were male. At diagnosis, 63% had detectable ctDNA [median: 5.3% (range: 0-43.1)]. Age, sex, race, ethnicity, and tumor size were not associated with a difference in ctDNA burden. Baseline detectable ctDNA burden (≥3%) was associated with an increased risk of EFS-event (relapse/progression, second malignant neoplasm, death) compared to undetectable ctDNA (2-year EFS: 56% [95% CI 45-68%] vs. 88% [95% CI 78-98%]; $P<$ 0.0001; **Table**). A similar pattern was seen using a cut point of ≥5% (53% [95% CI 41-67%] vs. 83% [95% CI 74-94%], $P<$ 0.0001). **Conclusions:** These findings validate prior data associating baseline ctDNA detection with inferior EFS in patients with localized osteosarcoma and identify the first prospectively validated molecular biomarker in this disease. Baseline ctDNA burden is now positioned for implementation into upcoming therapeutic trials of risk-stratified therapy in localized osteosarcoma. Research Sponsor: Conquer Cancer, the ASCO Foundation; Alex's Lemonade Stand Foundation; Boston Children's Hospital; Dana-Farber Cancer Institute; Harvard Catalyst Program; Khimani Fund; National Cancer Institute/U.S. National Institutes of Health; R37CA244355; QuadW.

	N (%)	2-year EFS (95% CI)	P-value
Detectable ctDNA			
< 3%	49 (37)	88% (78-98%)	< 0.0001
≥ 3%	84 (63)	56% (45-68%)	
Median ctDNA			
< 5%	64 (48)	83% (74-94%)	< 0.0001
≥ 5%	69 (52)	53% (41-67%)	

11511 Clinical Science Symposium

Impact of ATRX loss on survival and immune microenvironment in multiple sarcoma subtypes.

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Background: Sarcomas are heterogeneous mesenchymal malignancies often with few treatment options and poor outcomes. *ATRX* is commonly altered in sarcoma, with loss-of-function (LOF) mutations observed in up to 35% of cases. *ATRX* plays roles in DNA damage response, telomere maintenance, and epigenetic regulation. However, the impact of *ATRX* loss on sarcoma biology and the potential of *ATRX* mutation to serve as a prognostic biomarker in sarcoma are under investigation. **Methods:** The predominant alteration seen in *ATRX* in sarcoma is LOF mutation, thus tumor specimens were scored for presence or absence of ATRX staining by immunohistochemistry (IHC) in clinically-annotated tissue microarrays (TMAs) including 95 patients with uterine leiomyosarcoma (ULMS), 127 with soft tissue leiomyosarcoma (STLMS), 82 with undifferentiated pleomorphic sarcoma (UPS), and 84 with well-differentiated/dedifferentiated liposarcoma (WD/DDLPS). We also performed IHC staining using a panel of immune cell markers and checkpoints on the ULMS TMA, including CD8, CD20, CD68, PDL1, CTLA4, CD47, and CD163, among others. Kaplan-Meier analysis with log rank tests were used to assess the impact of ATRX loss on overall survival (OS), disease-specific survival (DSS), and progression free survival (PFS). Cox proportional hazards modeling was used to determine whether ATRX loss is an independent predictor of survival. T tests, ANOVA, and Chi squared tests were used to test for association between ATRX loss and immune markers in the ULMS TMA. **Results:** ATRX loss was seen in 14.1% of STLMS (n = 18), 52.6% of ULMS (n = 50), 36.6% of UPS (n = 30), and 8.3% of WD/DDLPS (n = 7). In univariate analysis, ATRX loss was associated with significantly worse OS (HR 0.50, 95% CI 0.31-0.80, p = 0.004) and PFS (HR 0.51, 95% CI 0.33-0.81, p = 0.004) in ULMS, worse DSS in UPS (HR 0.46, 95% CI 0.23-0.95, p = 0.03), and worse PFS in WD/DDLPS (HR 0.13, 95% CI 0.02-0.73, p = 0.02). In multivariate analyses, ATRX loss was also associated with worse OS and PFS in ULMS and worse DSS in UPS. In ULMS, ATRX loss was associated with increased density of CD8+ T cells (p = 0.01), PDL1 expression (p = 0.03), CTLA4 expression (p = 0.049), IDO-positive tumor cells (p = 0.01), and CD163-positive cells (p = 0.003). **Conclusions:** ATRX loss is associated with worse outcomes in ULMS, UPS, and WD/DDLPS. ATRX loss is also associated with a distinct immune microenvironment in ULMS characterized by T cell exhaustion and immunosuppressive M2 macrophages. Future work will focus on understanding the molecular underpinnings of these associations and potential ways to exploit these findings therapeutically. Research Sponsor: U.S. National Institutes of Health; T32 CA009666; U.S. National Institutes of Health; P30 CA016672.

11512 Rapid Oral Abstract Session

Phase II trial, multicenter, first line paclitaxel-avelumab treatment for inoperable angiosarcoma.

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Background: Angiosarcomas are very rare tumors of vascular or lymphatic origin characterized by a clinical heterogeneity in terms of presentation and behavior. It can occur in any site of body but most commonly originate in the skin of head and neck and in breast area. Many patients could not receive surgical resection due to its location and/or rapid progression, even who had localized disease. Moreover, conventional cytotoxic chemotherapy has shown limited effect in angiosarcoma. Here, we conduct a prospective, phase II study to evaluate the efficacy and toxicities of paclitaxel plus avelumab as the first line therapy for unresectable angiosarcoma. **Methods:** Patients with unresectable locally advanced or metastatic angiosarcoma, who had not received systemic treatment, were enrolled. Paclitaxel (80 mg/m^2) was intravenously infused on days 1, 8, and 15 of every 28-days cycle, and avelumab (10mg/kg) was intravenously infused biweekly. The treatment was continued until disease progression or unacceptable toxicity, or withdrawal of consent, whichever occurred first. The primary endpoint was the objective response rate (ORR), and the secondary endpoint was overall survival (OS), progression free survival (PFS), and safety profiles. **Results:** A total 32 patients (21 male, 11 female) were finally enrolled, and the median age was 63.5 (range, 27 to 82). The ORR was 50.0% (n = 16), including one complete response. Median OS and PFS were 14.5 (95% CI, 9.4 to 24.6) and 6.0 (95% CI, 5.4 to 9.5) months, respectively. Among patients who received at least one dose of treatment (n = 33), adverse events (AEs) of any grade were reported in 90.9% (n = 30), and severe AEs were in 12.1% (n = 4), including one death. The most common hematologic/non-hematologic AEs were neutropenia (n = 13, 39.4%) and pain (n = 12, 36.4%), respectively. Febrile neutropenia, neutropenia, and aspiration were reported in two patients (6.1%) each. **Conclusions:** Avelumab plus paclitaxel for patients with inoperable angiosarcoma, was effective and has tolerable safety profile. Additional translation studies and phase III studies are needed to clearly identify effectiveness and safety. Clinical trial information: NCT03512834. Research Sponsor: The healthcare business of Merk KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Best Response	n (%)
Complete response	1 (3.1%)
Partial response	15 (46.9%)
Stable disease	14 (43.8%)
Progressive disase	2 (6.2%)
Objective response rate	16 (50.0%)
Clinical benefit rate	30 (93.8%)
Overall survival	14.5 mo (95% CI, 9.4 - 24.6)
Progression free survival	6.0 mo (95% CI, 5.4 - 9.5)

11513 Rapid Oral Abstract Session

Cemiplimab in locally advanced and/or metastatic secondary angiosarcomas (CEMangio): A phase II clinical trial.

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Background: Angiosarcomas (AS) are rare and aggressive vascular sarcomas that can be subdivided in primary (de novo; pAS) and secondary AS (sAS). Secondary AS arise due to DNA damaging factors like radiotherapy (RT) and UV radiation or due to chronic lymphedema (Stewart Treves AS). Prognosis of locally advanced and metastatic AS is very poor and treatment options are limited. sAS differ from pAS in clinical behavior, genetic and molecular background. Instead, sAS show similarities to cutaneous squamous-cell carcinoma, for which the immune checkpoint inhibitor (ICI) cemiplimab showed impressive results. The high T-cell infiltrated tumor microenvironment and frequent DNA damage response mutations in sAS indicate susceptibility to ICI. Based on these tumor characteristics and anecdotical reports of responses to ICI in UV associated secondary AS, a clinical trial was designed with cemiplimab in sAS. **Methods:** In this prospective single arm multicenter phase II trial, the efficacy and safety of ICI cemiplimab 350 mg iv 3-weekly was investigated in patients with locally advanced or metastatic sAS. Using a Simons two-stage design, a total of 18 patients (pts) were included. The primary outcome is best overall response rate (BORR) after 24 weeks of cemiplimab treatment. Secondary outcomes include median time to response (mTTR), duration of response (mDOR), progression-free survival (mPFS), and overall survival (mOS) as well as translational biomarkers for response. Tumor mutational burden (TMB) and microsatellite instability (MSI) are investigated using "TruSight Oncology 500" (Illumina) sequencing (n = 16). In samples with high TMB (≥10 mutations / Megabase (Mb)), the mutational signature is analyzed. **Results:** At the cutoff date (23-Jan-24) all 18 projected pts have been included (12 RT-sAS, 3 UV-sAS, 3 Stewart Treves sAS). Cemiplimab was first line treatment in 10 pts (55.6%), second line in 6 pts (33.3%) and third line in 2 pts (11.1%). Median follow-up time was 8.0 months. The BORR at 24 weeks was 27.8%, with partial response (PR) in 4 patients (2 RT-sAS and 2 UV-sAS) and 1 complete response (CR) in a RT-sAS. One patient with a PR at 24 weeks (UV-AS) developed a CR. In both patients CR is ongoing. The mTTR was 2.6 months (range 1.2-5.4) and mDOR 6.2 months (range 0.43-N/A). The mPFS was 4.1 months (95% CI 1.2-6.4) and mOS was not reached. The toxicity profile was as expected. Three patients stopped treatment due to ICI related toxicity (1 pt with hepatitis grade 3, 1 pt with hepatitis grade 4, and 1 pt with dermatitis grade 2). High TMB was observed in 3 pts with UV-sAS, all showing single-base substitution signature 7a, associated with UV damage. The 2 pts with the highest TMB (60 and 125 mut/Mb) showed PR as BORR at 24 weeks. None of the patients showed MSI. Results of the additional biomarkers will be available at the ASCO meeting. **Conclusions:** Cemiplimab shows promising effectivity in secondary angiosarcomas. Clinical trial information: NCT04873375. Research Sponsor: Genzyme Europe B.V.; Sarcoma Foundation of America; Radboud University Medical Center.

11514 Rapid Oral Abstract Session

Alliance A091902: A multicenter randomized phase II trial of paclitaxel (P) with or without nivolumab (N) in patients (pts) with advanced angiosarcoma (AS).

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Background: The role of immunotherapy remains uncertain in most sarcomas. We recently showed significant antitumor benefit for cabozantinib (C) with N in AS previously treated with a taxane. Since chemotherapy-immunotherapy combinations may synergize, and paclitaxel remains a standard of care option for advanced AS, we hypothesized that P+N would be more effective than P alone. **Methods:** We report Arm 1 (P+N) and Arm 2 (P) of this open label, multi-arm, phase II study. Pts all had locally advanced/metastatic AS, and no prior taxane (including adjuvant) or checkpoint inhibitor prior to entry. Pts were randomized 1:1 (stratified scalp/face vs other) to receive P 80 mg/m2 on days 1, 8, 15 every 4 weeks (wks), with (Arm 1) or without (Arm 2) N (480 mg intravenously every 4 wks). A pt could remain on study beyond disease progression (PD), after the initial 12 wk evaluation (4 wk confirmatory scan required), but responses were censored at 12 wks. Primary endpoint was progression-free survival (PFS) comparing P+N to P, with an assumed improvement from a median of 4 to 7 months with N added to P (power = 85.3%, alpha = 0.148, and one interim analysis (Wieand rule) for futility planned after 30 events). Secondary endpoints were overall response rate (ORR), adverse events (AEs), overall survival (OS), and pt reported outcomes (PRO). At PD, Arm 2 (P) pts were permitted to receive C+N. **Results:** 62 evaluable pts (P+N = 30, P = 32 pts) were balanced for age, race, ECOG PS 0 vs. 1, site of disease (including radiation related vs. not), while P+N had more females (60%) and P had more males (63%). Median PFS for P+N was 7.2 mo (5.3-17 mo), and 8.3 mo (4.0-18 mo) for P (hazard ratio (HR) 1.01 (95%CI: 0.55-1.9), p = 0.96). Median PFS for scalp/face was 16 mo (95%CI: 10-NR) for P+N and 8.3 mo (95%CI: 3.7-NR) for P. Median PFS for all others was 5.5 mo (95%CI 4.3-16) for P+N, and 6.0 mo (95%CI 4.1-NR) for P. Median OS was 18 mo (13-NR) in P+N, and 23 mo (15-NR) in P (HR 1.3 (95%CI: 0.63-2.7), p = 0.48). Overall confirmed ORR: P+N = 33% (10/30 pts, with 4 partial responses (PR) and 6 complete responses (CR) with scalp/face ORR = 73%, all others ORR = 11%). Overall ORR for P = 34% (11/32 pts, with 7 PR and 4 CR, with scalp/face ORR = 38%, all others ORR = 26%). Grade 3-4 AEs regardless of attribution occurred in 57% of P+N, and 44% of P, most commonly ($>$ 10%) fatigue, AST increase, and dyspnea for P+N (n = 3 each), and anemia (n = 4) for P. **Conclusions:** P alone can be an effective therapy in a subset of pts with AS. The combination of P+N failed to demonstrate improvement in median PFS over P alone, but may show benefit in scalp/face AS. OS trended better with P alone. No new safety signals were observed. The impact of weekly steroid premedication prior to P+N on these outcomes remains to be determined. PRO and exploratory analyses are ongoing. Support: U10CA180821, U10CA180882, U24 CA196171; NCT04339738.https://acknowledgments.alliancefound.org. Clinical trial information: NCT04339738. Research Sponsor: National Cancer Institute.

11515 Rapid Oral Abstract Session

A phase II study of anlotinib and an anti-PDL1 antibody in patients with alveolar soft part sarcoma: Results of expansion cohorts.

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Background: The combination of the anti-angiogenesis tyrosine kinase inhibitor (TKI), anlotinib, with the anti-programmed death-ligand 1 (PDL1) antibody (TQB2450) demonstrated commendable antitumor efficacy in a phase II clinical trial for pan-sarcoma patients, particularly within the alveolar soft part sarcoma (ASPS) cohorts (Liu et al., 2022, PMID: 35675031). An expansion of the ASPS cohort has been underway since 2019. Herein, we present the observed efficacy within this ASPS-specific expansion cohort. **Methods:** ASPS patients naïve to TKIs or immunotherapy received TQB2450 (1200mg) intravenously on day 1, in combination with oral administration of anlotinib (12mg) from day 1 to 14, repeated every 3 weeks. The primary endpoint was best objective response rate (ORR, per RECIST v1.1). Secondary endpoints comprised median progression free survival (PFS), median overall survival (OS), duration of response (DOR), and adverse events (AEs). Formalin-fixed paraffin-embedded (FFPE) slides were taken for immunohistochemistry and examined for lymphocyte marker expression. **Results:** Twenty-nine patients were enrolled in the phase II trial. The median age was 29 years (range: 19-46), with female 48.3%. A subset of patients (20.7%) had undergone prior lines of chemotherapy. Twenty-eight patients were evaluable for efficacy (one withdrew). The ORR for evaluable patients reached 79.3%, characterized by 3 complete responses and 20 partial responses. The median PFS (months) was not reached (95%CI: 20.7, not-reached). The median DOR (months) for responders was not reached (95%CI: 18.0, not-reached). No mortalities occurred during the follow-up. Treatment demonstrated favorable tolerability, with predominant grade 1 and 2 AEs. Thirteen patients (44.83%) experienced grade ≥3 AEs, principally hypertriglyceridemia (13.79%), lipase elevation (6.90%), amylase elevation (3.45%), and hypertension (3.45%). A detailed analysis of the tumor microenvironment in 7 patients, including 3 good responders and 4 poor responders, revealed a significant discrepancy in the presence of tertiary lymphoid structures (TLS) between the two groups (refer to Table). **Conclusions:** The combination of anlotinib and TQB2450 exhibits promising efficacy in ASPS patients, markedly enhancing ORR and extending PFS with favorable tolerability. Notably, TLS emerges as a potential predictive indicator of immunotherapeutic efficacy in ASPS. Clinical trial information: CTR20190938. Research Sponsor: None.

Lymphocyte Marker /Mean Number Per mm^3	Good Responders (n = 3)	Poor Responders (n = 4)	*P* value
CD3	589	1074	0.49
CD4	133	369	0.20
CD8	392	746	0.62
CD68	216	64	0.59
CD163	752	947	0.47
PD1	358	536	0.75
PDL1	1.67	17.5	0.48
TLS	0.48	0.05	**0.04**

11516 Rapid Oral Abstract Session

Reshaping the tumor microenvironment of cold soft-tissue sarcomas with anti-VEGFR targeted therapy: A Phase 2 Trial of Regorafenib combined with avelumab.

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Background: Vascular Endothelial Growth Factor (VEGF)-driven angiogenesis is a pivotal factor in creating an immunosuppressive tumor microenvironment. Approximately 80% of Soft Tissue Sarcomas (STS) are characterized by a 'cold' microenvironment, lacking tertiary lymphoid structures (TLS). While the efficacy of VEGF pathway and PD-1/PD-L1 axis blockade has been established in various tumor types, their impact on 'cold' STS remains unexplored. This study aims to evaluate the synergistic effect of anti-angiogenesis and PD-1 blockade in altering the microenvironment of cold STS, potentially enhancing immune response and therapeutic efficacy. **Methods:** In this phase II, single-arm, open-label, multicentric trial, we explored the efficacy and safety of combining regorafenib (R) and avelumab (A) in advanced TLS-negative STS patients. Patients were administered 160 mg of R daily for 3 weeks in a 4-week cycle, alongside 10 mg/kg of A biweekly. Endpoints included high-throughput analysis of tumor and plasma samples, response rate, progression-free survival (PFS), overall survival (OS), and safety, as per the NCI-CTCAE v5.0 guidelines. **Results:** From May 2019 to August 2021, 49 TLS-negative STS patients were enrolled, including leiomyosarcoma (45%), synovial sarcoma (18%), and other subtypes. The median age was 57.1 years, with patients having undergone an average of 2 prior treatment lines. High-throughput analysis of sequential plasma samples indicated an upregulation of immune-inducing protein biomarkers such as CXCL10 and soluble CD8 antigen. Multiplex immunofluorescence analysis of sequential tumor samples revealed significant increase in CD8 T cell infiltration on-treatment. The most common severe adverse events were grade 1 or 2 palmar-plantar erythrodysesthesia, fatigue, and diarrhea. The median follow-up was 7.1 months, with 32.6% of patients experiencing tumor shrinkage, and a clinical benefit rate of 48.8%. The 6-month PFS was 22.1%, with a median OS of 15.1 months. **Conclusions:** The combination of regorafenib and avelumab demonstrates a marked mobilization of antitumor immunity in patients with TLS-negative STS. The observed efficacy appears superior to that of single-agent immune checkpoint inhibition in 'cold' STS, and higher than the 6-month PFS benchmark of 14% set by EORTC. This indicates the potential effectiveness of this treatment combination in managing advanced cold STS, marking a significant stride in precision immunotherapy for this group of tumors. Clinical trial information: NCT03475953. Research Sponsor: BAYER; MERCK.

11517 Rapid Oral Abstract Session

A phase 2, single arm, European multi-center trial evaluating the efficacy of afatinib as first line or later line treatment in advanced chordoma.

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Background: EGFR and Her2 overexpression in chordoma is well known, and chordoma cell-lines and mouse models were proven to be sensitive to EGFR inhibitor afatinib. This phase 2, single arm, European multi-center trial was designed to evaluate the efficacy of afatinib as first- or later-line tyrosine kinase inhibitor (TKI) treatment in advanced chordoma. Here we report efficacy and safety data. **Methods:** Eligible patients (pts) had locally advanced or metastatic, pathologically proven, EGFR expressing chordoma, not amenable for local therapies, with confirmed measurable and progressive lesions according to RECIST1.1. Pts were treated with afatinib 40mg/day in a 4 week cycle until disease progression (PD), unacceptable toxicity or withdrawal. Radiological tumor response assessment was performed every 3 cycles. The primary endpoint was response defined as progression free survival (PFS) rate ≥12 months (mos) for first-line cohort 1 and ≥ 9 mos for further-line treatment cohort 2, and change from baseline in EORTC QLQ- C30 and Brief pain inventory (BPI) questionnaires. Pts were enrolled using a Simon's two-stage design, enrolling 13 patients in stage one, ≥3 patients with a PFS ≥ 12 or 9 mos were needed to enter stage two, where 43 pts total were to be enrolled, and ≥13 free from progression at 9 or 12 mos were required to meet the primary endpoint for success. **Results:** From Jun 2018 to Oct 2022, 47 pts were included. Four were ineligible for efficacy analysis (1 withdrawal, 3 stopped due to toxicity before first radiological evaluation). 34 entered cohort 1, 13 cohort 2. 31 (66.0%) were men, median age was 53 (range 28-85) years. 16 (34.0%) pts received prior systemic therapy (3 chemotherapy, 13 TKI, 2 immunotherapy, 2 other). The PFS rate at 12 mos was 40.0% in cohort 1 (12/30 pts), and 38.5% in cohort 2 (5/13 pts). Overall median PFS was 8.6 mos (95% CI 5.6-13.6); 9.1 mos (95% CI 5.8-16.6) in cohort 1 and 7.1 mos (95% CI 2.8-16.5) in cohort 2. Two pts remained on treatment at time of analysis. Best objective response by RECIST 1.1 was partial response in 4 pts (9.3%), stable disease in 33 (76.7%), PD in 5 pts (11.6%) and 1 (2.3%) unknown due to clinical progression. Median follow-up time was 23.7 mos (interquartile range 11.0-21.2). 16/47 pts (30.4%) experienced grade ≥3 adverse events (AEs). No grade 5 AEs related to afatinib were reported. Most common grade 3-4 afatinib-related AEs were skin toxicity (10.6% of pts), diarrhea (10.6%), mucositis (6.4%), hypertension (4.3%). Dose reduction was needed in 20/47 (42.6%) pts, and at least one dose interruption was needed in 31/47 (66.0%) pts. **Conclusions:** With a PFS rate at 12 mos of 40.0% in the first-line cohort and 38.5% at 9 mos in the further-line cohort, this phase 2 study met the PFS endpoint. QoLQ data will be provided at the conference . Partial response by RECIST was seen in 4/43 pts. Toxicity and dose reductions were relevant but manageable in most pts. Clinical trial information: NCT03083678. Research Sponsor: Boehringer Ingelheim; 1200-0277; Chordoma Foundation; NIHR UCLH Biomedical Research Centre.

11518 Rapid Oral Abstract Session

Phase 1 study of NB003, a broad-spectrum KIT/PDGFRα inhibitor, in patients with advanced gastrointestinal stromal tumors (GIST).

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Background: NB003 is a potent and selective small-molecule tyrosine kinase inhibitor of KIT/PDGFRα. It was designed to inhibit a broad spectrum of primary and acquired imatinib-resistant mutations in KIT/PDGFRα. **Methods:** This is a first-in-human phase 1 study in patients (pts) with advanced GIST who progressed on or intolerant to imatinib and other SoCs. Pts received oral NB003 twice daily (BID). An accelerated titration followed by a Bayesian optimal interval (BOIN) design was used. After the MTD or MAD was determined, putative RP2D(s) were explored to establish the RP2D. The primary endpoint was safety and tolerability. Other endpoints included PK, efficacy and mutational status by ctDNA. **Results:** As of Jan 10, 2024, 42 pts (median age 55 y [range 33–81]; 69% male; 71.4% ECOG PS 1; 69% primary mutation in KIT exon 11; median 4 prior TKI therapies [range 2–7]) were treated in dose escalation phase. Seven dose levels (DL) were tested, including 3mg (1 pt), 6mg (1 pt), 12mg (3 pts), 20mg (15 pts), 30mg (15 pts), 35mg (4 pts), 40mg (3 pts). The most frequent treatment-related adverse events (TRAEs) were asymptomatic CPK increased (92.9%), anaemia (78.6%), AST increased, face oedema, WBC decreased (76.2% each), periorbital oedema (66.7%), neutrophil count decreased (64.3%), amylase increased (57.1%), lipase increased (52.4%), platelet count decreased (45.2%), oedema peripheral (38.1%). The most frequent Grade ≥3 TRAEs were anaemia (61.9%), asymptomatic CPK increased (59.5%), neutrophil count decreased (23.8%), WBC decreased (21.4%). TRAEs leading to treatment discontinuation were reported in 2 pts (fatigue, tumor haemorrhage) at 20mg DL, 2 pts (AST increased, WBC decreased) at 30mg DL and 1 pt (face oedema) at 40mg DL, respectively. DLTs occurred in 2 pts at 40mg DL (fatigue, face oedema) and 2 pts at 30mg DL (febrile neutropenia, rash maculo-papular, AST increased). In 42 treated pts, the confirmed ORR was 26.2% (11/42, 95% CI:13.9, 42.0) per mRECISTv1.1 by investigator assessment, DCR was 73.8% (31/42, 95% CI:58.0, 86.1). Most of the responses (7/11) are still ongoing. Tumor responses were observed in pts with a broad spectrum of acquired resistance mutations in both ATP-binding site and activation loop of the kinase domain of KIT based on predose ctDNA (including 3 pts with exon11/13, 3 pts with exon11/17, 2 pts with exon17, 1 pt with exon16, 1 pt with exon 9/17, 1 pt not detected). A correlation is observed between changes in the KIT mutation allele fraction (MAF) in ctDNA and changes in tumor size from baseline. **Conclusions:** In heavily pretreated pts with advanced GIST, NB003 demonstrated a manageable safety profile with encouraging antitumor activity across a broad spectrum of secondary resistance mutations in KIT. The RP2D was defined as 20mg BID based on overall safety and efficacy. Expansion cohorts in different lines of GIST are currently under enrollment. Clinical trial information: NCT04936178. Research Sponsor: None.

11519 Rapid Oral Abstract Session

Durvalumab and tremelimumab versus doxorubicin in previously untreated patients with advanced or metastatic soft tissue sarcoma: Patient-reported outcomes (PROs) of the randomized phase II MEDISARC study (AIO-STS-0415).

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Background: The randomized phase II MEDISARC trial (NCT03317457) tested durvalumab (DUR) and tremelimumab (TRE) vs. doxorubicin (DOX) in soft tissue sarcoma (STS) patients in first-line therapy. The study showed no PFS benefit (HR 1.22; 95%CI 0,90-1.64; P = .4049), but a trend in prolonged OS (HR 0.73; 95%CI 0.54-0.99; P = .185) in favor of DUR-TRE (Grünwald et al. ESMO 2024: LBA90). The current analysis reports on patient reported outcomes (PROs) under treatment. **Methods:** We utilized EORTC QLQ-C30 printed questionnaires in randomized patients. PRO were assessed during screening and under treatment every 12 weeks until progression, and 4 weeks after last dose. Time to deterioration (TTD; decrease by 5 points) and mean change from baseline was measured for QLQ-C30 domains. Formal statistic testing was not performed. **Results:** The median follow-up for DUR-TREM vs. DOX were 34.0 mo. (25.6-42.2) and 37.9 mo. (31.5-37.9). The median duration of therapy was 2.8 (0-13) and 2.1 (0-4) mo., respectively. 86 of 92 (93.5%) patients had ≥1 PRO assessments and were included into the analyses. The completion rate at week 12 was 41.3%. Mean baseline global health status (GHS) was 54.1 (SD: 25.64) and 56.5 (SD: 28.47), respectively. GHS above the median was associated with improved OS and PFS in both arms, indicating a possible predictive biomarker. Under treatment, changes in PRO domains at 12 weeks were noted. TTD favored DUR-TRE in selected functional and symptom domains. Details will be shown at the meeting. **Conclusions:** MEDISARC is the first study to compare check-point inhibitor and doxorubicin treatment in sarcoma patients. PRO measures from baseline to week 12 favored DUR-TRE. Overall, results indicated better symptom and quality of life in patients treated with DUR-TRE. Clinical trial information: NCT03317457. Research Sponsor: AstraZeneca.

	DUR-TRE (n = 53)	DOX (n = 39)
GHS: Mean baseline (SD)	54.1 (25.64)	56.5 (28.47)
GHS: Mean change at week 12 (SD)	-0.6 (18.47)	-10.6 (18.03)
OS: Above median baseline GHS, mo (95%CI)	27.6 [10.3-40.6]	13.0 [10.8-25.4]
OS: Below median baseline GHS, mo (95%CI)	9.7 [3.2-17.5]	7.9 [3.5-15.6]
PFS: Above median baseline GHS, mo (95%CI)	2.9 [2.6-3.5]	3.1 [2.7-7.0]
PFS: Below median baseline GHS, mo (95%CI)	2.4 [2.0-2.8]	2.7 [1.3-7.9]

11520 Rapid Oral Abstract Session

Monitoring ovarian function in oncology studies: Results and insights from the DeFi phase 3 study of nirogacestat in desmoid tumor.

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Background: Initiated in 2019, DeFi (NCT03785964) was a phase 3 study that incorporated comprehensive assessment of ovarian function prior to the 2023 ASCO guidance (Cui et al. *Lancet Oncol*) on assessing ovarian toxicity (OT) in oncology clinical trials. In DeFi, OT was identified as a safety signal with nirogacestat (niro), a selective gamma secretase inhibitor FDA-approved for adults with progressing desmoid tumors. We provide results and insights in assessing OT in females of reproductive potential (FORP) from DeFi. **Methods:** Patients were randomized to twice-daily oral niro or placebo (pbo). Investigator-identified OT and resolution in FORP were based on abnormal reproductive hormone values (increased follicle-stimulating hormone [FSH] or luteinizing hormone; decreased progesterone, anti-Müllerian hormone [AMH], or estradiol) assessed via scheduled testing, perimenopausal symptoms, or both. Based on the ASCO guidance, patient-level post hoc analyses included return of menses and last-reported FSH levels to within normal limits (WNL; ≤20.4 mIU/mL). **Results:** In the DeFi safety population, 73 were FORP (niro = 36, pbo = 37). Investigators identified OT in 0% of FORP receiving pbo and 75% (27/36) receiving niro. As of Oct2022, investigators reported that OT resolved in 78% (21/27): 100% (11/11) after stopping niro treatment for any reason (4 discontinued niro due to OT) and 71% (10/14) while remaining on niro; 2 were lost to follow-up. Of the 11 patients with off-treatment resolution, all met at least one of the recommended ASCO criteria for assessing OT resolution; all 9 with available menstruation information experienced return of menses and 8 had FSH WNL. Insights: Study limitations included timing of hormonal assessments (scheduled to study visits and not menstrual cycle), lack of menstrual diaries, and incomplete hormone assessments for some patients. Capture of OT can pose challenges, as MedDRA coding may not reflect adverse events observed in the female reproductive system. Further, hormone levels during DeFi could have been impacted by baseline ovarian function and prior use of gonadotoxic drugs/multiple lines of therapy. Hormone measures in clinical studies are important to determine a drug's effects on ovarian function. However, there is presently no scientific consensus for hormone monitoring during cancer therapy or niro treatment in clinical practice. Ultimately, it is important to understand the patient's fertility goals and to monitor ovarian function during oncology clinical trials. **Conclusions:** In DeFi, 75% of FORP treated with niro experienced OT. Most events resolved, including in 100% who stopped treatment for any reason, suggesting OT with niro is transient. Though initiated prior to the ASCO guidance, OT assessments in DeFi generally align with and support the use of both clinical measures and hormone biomarkers in oncology clinical trials. Clinical trial information: NCT03785964. Research Sponsor: SpringWorks Therapeutics, Inc.

11521 Poster Session

Feasibility and tolerance of high-dose methotrexate (HDMTX) in older patients with osteosarcoma.

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Background: Osteosarcomas (OS) comprise the majority of new primary bone tumors in the US and affect a bimodal distribution of young adults (2nd-3rd decades) and older adults >65 yrs. Most large collaborative studies demonstrating the efficacy of HDMTX-containing chemotherapy regimens in OS limited enrollment to patients <40 yrs. Our study aims to fill the gap of reported clinical outcomes in adult OS patients ≥ 40 yrs by describing the feasibility and tolerability of HDMTX in these patients at Mayo Clinic. **Methods:** We conducted a retrospective chart review of patients ≥18 yrs with OS seen at our institution between 1/1/1980-9/30/2019 and who received ≥1 dose of HDMTX (12 g/m^2, max 20 g). Extraosseous OS were excluded. Survival analyses were run for both the entire study population and the subset of patients age ≥40. Patient demographics, disease characteristics, and clinical outcomes were collected. The primary outcome evaluated was 5-year overall survival (5-yr OS). **Results:** We identified 94 patients whose demographic data are summarized (Table). Twenty-three of 94 (24%) were ≥40 yrs. Both the median number of HDMTX doses received and number of patients who received ≥50% recommended doses were significantly less among patients ≥40 yrs. However, HDMTX-related AKI and median number of hospital days did not differ significantly between the age groups. Among all patients, 5-yr OS was significantly improved (p=0.0025) at 45% (95% CI 35%-58%) for those who received ≥50% doses HDMTX compared to 5-yr OS of 25% (95% CI 12%-53%) for those who did not. Among patients ≥40 yrs, 5-yr OS was significantly improved (p=0.017) at 86% (95% CI 63%-100%) for those who received ≥50% doses HDMTX compared to 5-yr OS of 31% (95% CI 14%-68%) for those who did not. **Conclusions:** In our cohort, 5-yr OS was superior in those patients who received at least 50% of the planned doses of HDMTX. Older adults were significantly less likely to receive the majority of planned doses, which may be due to clinician bias regarding anticipated toxicity. However, we show that common HDMTX-associated toxicities did not vary significantly by age. If feasible, we recommend referring older patients with osteosarcoma to centers equipped to handle the staffing and supportive care needs of HDMTX administration. Research Sponsor: None.

	Age Group		
	18-39 (n=71)	≥40 (n=23)	*P*-value
Male sex, *n (%)*	41 (58)	16 (70)	0.34
Appendicular tumor location, *n (%)*	54 (76)	18 (78)	1
Median tumor max dimension (cm),n (range)	8 (1-37)	7.5 (2-20)	0.44
Baseline CKD stage ≤ 2, n (%)	56 (79)	23 (100)	0.10
Median HDMTX doses,n (range)	9 (1-16)	4 (1-11)	<0.001*
Received ≥50% planned HDMTX doses, *n (%)*	67 (94)	7 (30)	<0.001*
MTX-related AKI,n (%)	2 (3)	3 (13)	0.09
Median Hospital Days for HDMTX administration, n (range)	4 (3-21)	5 (3-21)	0.29
Histologic response ≥90% necrosis, *n (%)*	22 (36)	3 (13)	0.18
Median OS,months (range)	Undefined (7-279+)	91 (3-122+)	0.14

11522 Poster Session

Preliminary results from FLAGSHP-1: A phase 1 study of ERAS-601 as a monotherapy or in combination with cetuximab in patients (pts) previously treated for advanced chordoma.

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Background: SHP2 is an oncogenic tyrosine phosphatase that transduces receptor tyrosine kinase signaling in the RAS/MAPK pathway via phosphatase-mediated regulation of guanine nucleotide exchange factors. SHP2 signaling has recently been identified as a genetic dependency for chordoma, a rare tumor type with no approved therapies (1), and preclinical studies with SHP2 inhibitors have demonstrated activity in chordoma models. **Methods:** As part of the FLAGSHP-1 study, patients (pts) with advanced or metastatic chordoma were enrolled in either the monotherapy or cetuximab combination cohort to assess the safety, tolerability, PK, and preliminary clinical activity of ERAS-601. Chordoma pts previously treated with an EGFR inhibitor were allowed to enroll. **Results:** As of 31 Oct 2023, a total of 11 pts with previously treated advanced or metastatic chordoma received ERAS-601. Two pts received ERAS-601 as monotherapy: one at 40 mg BID (continuous) and the other at 80 mg TIW (three times a week). An additional 9 pts received the combination of ERAS-601 (40 mg BID 3 weeks on and 1 week off every 28 days [3/1]) in combination with cetuximab (500 mg/m2 Q2W). The treatment-emergent adverse events (TEAEs) occurring in >20% of pts (Grade [Gr] 1-2 unless noted) were: dermatitis acneiform (2 pts-Gr 3), paronychia, dry skin, skin fissures, skin infection (1 pt-Gr. 3), diarrhea, nausea, vomiting, stomatitis, peripheral oedema, fatigue, thrombocytopenia, and AST elevation. No patients discontinued therapy due to TEAEs related to ERAS-601. Out of the 9 pts receiving the combination of ERAS-601 and cetuximab, by RECIST 1.1 there was 1 PR and 8 pts with a best response of SD. Of the 8 pts who had a best response of SD, 7 had some tumor shrinkage. The median time on combination treatment was 5.06 months, with 8 out of 9 pts remaining on the study. **Conclusions:** The most common toxicities observed for the ERAS-601 + cetuximab combination were dermatologic, which were reversible. Encouraging preliminary activity was seen in advanced, refractory chordoma. 1. Sharifina et al., 2023, Nat. Commun. Clinical trial information: NCT04670679. Research Sponsor: None.

11523 Poster Session

Transcriptomic analysis of novel tumor suppressor gene fusions in bone sarcomas.

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Background: Despite the evolution of therapeutic strategies for sarcomas in the past four decades, survival in the metastatic setting remains poor. This underscores the urgent need to explore new diagnostic and treatment avenues to improve patient outcomes. Harnessing the capability of RNA sequencing (RNA-seq) to detect gene fusions de-novo, we analyzed treated bone sarcoma samples with the aim to uncover gene fusions and breakpoints that are potentially relevant as clinical biomarkers and treatment targets. **Methods:** We analyzed 83 formalin-fixed, paraffin-embedded tumor samples of treated bone sarcomas, including osteosarcomas, chondrosarcomas, chordomas, and Ewing sarcomas. These samples were subject to in-depth whole exome analysis and bulk RNA-seq. RNA-seq was employed to identify gene fusions, with STAR-fusion utilized for sequence calling. Quality control of all NGS samples was performed using FastQC, FastQ Screen, RSeQC, and MultiQC. Tumor purity was assessed via pathological and bioinformatics examination with the threshold set at 20%. Fusions involving tumor suppressor genes listed in the OncoKB database were investigated further. A comprehensive literature search on PubMed and Google Scholar as well as analysis of the FusionGDB and COSMIC databases were performed to verify candidates of novel gene fusions. We also compared our samples with those in the publicly available MSK sarcoma cohort and 11 osteosarcoma cell line datasets. **Results:** We detected 238 gene fusions in all samples analyzed. Among these fusions, 18 (16 previously unknown, 2 previously reported) involving known tumor suppressor genes were present in 14 samples (17%). Among the 16 previously unknown fusions, 8 were indicative of potential loss-of-function variants of tumor suppressors: *TP53-NF1*, *TP53-CEMIP*, *CTNNBL1-RB1*, *PRPF40A-FBXW7*, *VAMP2-MSH3*,and *ETV6-ATM* in osteosarcoma; *BRD4-TP53* in unspecified bone sarcoma; and *FBXW7-ZNF770* in Ewing sarcoma. Furthermore, we also uncovered a novel breakpoint combination in *EWSR1-ETV4* in Ewing sarcoma that links exon 9 of *EWSR1*to exon 9 of *ETV4*. **Conclusions:** Our comprehensive transcriptomic analysis of treated sarcoma samples uncovered previously unknown gene fusions involving tumor suppressor genes and a unique breakpoint combination in an oncogene. These findings emphasize the crucial role of RNA-seq not only in advancing genomic research of sarcomas, but also in identifying potential biomarkers/targets and devising new treatment strategies for this rare cancer. Research Sponsor: None.

11524 Poster Session

Extracorporeal irradiation and reimplantation for bone sarcomas: Medium- and long-term oncologic and functional outcomes.

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Background: Extracorporeal irradiation is an effective and established method for limb salvage in the management of malignant bone tumours.We analyzed the oncological and functional outcomes of extracorporeal radiotherapy (ECRT) and reimplantation done for bone sarcomas. **Methods:** 67 patients (29 osteosarcoma, 27 Ewing's sarcoma, 11 others; mean age 16 years) were treated with ECRT between 2010 and 2022. Femur was commonest bone (33) followed by tibia (11) and humerus (11). 48 had a metadiaphyseal while 19 had osteoarticular resections. A single dose of 50 Gy was delivered to the resected bone segments. The irradiated bones were reimplanted immediately as a biological graft. Construct was stabilized with long locking plates. Osteoarticular ECRT was coupled with joint replacement. Patients were treated with chemotherapy as per standard protocol. Functional outcome was assessed by Musculoskeletal Tumor Society (MSTS) scoring system. **Results:** The mean resected length of bone was 17 cm (9 to 26). All 67 patients were available at a mean follow-up of 66 months (22 to 166). The mean time to union for all osteotomy sites was 6 months (2 to 17): metaphyseal osteotomy sites united quicker than diaphyseal osteotomy sites (3.8 months (3 to 6) versus 9.5 months (4 to 17)). 2 deep infections necessitated removal of the ECRT segment. There were 2 local recurrences in soft-tissue needing amputation. 6 of the remaining 113 (5.3%) junctions remained ununited which needed additional bone grafting. 5/6 junctions united after bone grafting. 1 remained ununited needing cementation across the segment. At the time of final follow-up, 47 patients were free of disease, one was alive with disease and 19 had died of disease. The mean Musculoskeletal Tumor Society Score at the last follow-up was 26 (18 to 30). **Conclusions:** The radiated bone acts as a size-matched allograft and has very good union rates. The complication rates are very low. Extracorporeal irradiation is an oncologically safe and biological reconstruction technique for limb salvage in sarcomas and has good functional results. It should be recommended to all suitable patients. Research Sponsor: None.

11525 Poster Session

Phase 1 results of the WEE1 inhibitor, azenosertib, in combination with gemcitabine (gem) in adult and pediatric patients (pts) with relapsed or refractory (R/R) osteosarcoma.

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Background: Patients with R/R osteosarcoma have poor outcomes with a historical 16-week event-free survival (EFS) of ~12% after treatment with salvage therapy (Lagmay et al, 2016). Azenosertib is a highly selective WEE1 inhibitor that induces cancer cells to accelerate through the G1/S and G2/M checkpoints without repairing damaged DNA, causing mitotic catastrophe and cell death. Azenosertib has demonstrated significant synergy with gem in non-clinical models. The purpose of this study was to evaluate the safety and tolerability, determine the maximum tolerated dose (MTD), and assess for anti-tumor activity in pts with R/R osteosarcoma receiving C and gem. **Methods:** This dose-finding study (NCT04833582) assessed azenosertib + gem in pts ≥12 years of age using a standard 3+3 design. The MTD was defined as the dose level with prespecified adverse events (dose-limiting toxicities [DLTs]) occurring at a rate <33%. The primary endpoint was the incidence and severity of DLTs in cycle 1. Secondary endpoints included the incidence and severity of adverse events and EFS at 18-weeks per RECIST v1.1 (time from treatment initiation until disease progression or death due to any cause). Pts were treated across 5 dose-finding cohorts, receiving azenosertib (starting dose 200 mg QD PO on a continuous schedule) and gem (starting dose 1000 mg/m^2 IV on D1 and D8 of a 21D cycle) until disease progression or unacceptable toxicity. **Results:** As of Nov 30, 2023, 31 pts had been treated. The median age was 27y (range 12-76); 21 (68%) pts were ≤39y. Pts received a median of 3 (1-9) prior therapies. At tolerated doses, the most frequent grade ≥3 adverse events (≥20%) included thrombocytopenia and lymphopenia (33% each); there were no grade 4 thrombocytopenia events or instances of febrile neutropenia. DLTs included thrombocytopenia and gastrointestinal toxicity. The MTD was determined to be azenosertib 150 mg daily on a 5:2 schedule (5 days on, 2 days off) + gem 800 mg/m^2. None of the pts treated at the MTD (n=6) required dose reductions of azenosertib due to AEs and only 1 required a dose interruption. The 18-week EFS was 39% (11/28) across all dose levels. **Conclusions:** Azenosertib + gem was well tolerated at the MTD and provided a greater EFS than historical control cohorts of salvage therapy in pts with R/R osteosarcoma. The MTD of the combination was well tolerated and these data support further investigation of azenosertib with gem in pts with R/R osteosarcoma in an upcoming Investigator-Initiated Phase 2 trial. Clinical trial information: NCT04833582. Research Sponsor: None.

11526 Poster Session

Correlative results from NCI CTEP/ETCTN 10330: A phase 2 study of belinostat with SGI-110 (guadecitabine) or ASTX727 (decitabine/cedazuridine) for advanced conventional chondrosarcoma (cCS).

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Background: There are no FDA-approved treatments for advanced cCS. Chemotherapy provides limited benefit. *IDH1/2* mutations (m) occur in 50% of cCS. Both *IDH*m and wild-type cCS harbor epigenetic dysregulation. In preclinical models, HDAC + DNMT inhibition (i) suppressed growth by inducing apoptosis, reversing the hypermethylated state, and upregulating expression of interferon (IFN) response genes including *PDL1*(1). This prompted a phase 2 study of HDACi + DNMTi in cCS, which failed to meet the 1° endpoint of ORR. The majority of pts had a best response of stable disease, with a trend towards improved mPFS in *IDH*m (2). Here we report correlative analysis of NCI 10330. **Methods:** NCI 10330 is a single-arm, multicenter, phase 2 study of belinostat with SGI-110 or ASTX727 in advanced cCS. All pts were required to have pre- and on-treatment (tx) biopsies (Cycle 2, Day 3-5). Tissue was evaluated with whole exome sequencing (WES) and RNA sequencing (RNAseq). From RNAseq, Tumor Inflammation Signature Scores (TISS) and Tumor Microenvironment functional Gene Set Enrichment Analysis scores (TME GSEA) were calculated as the mean of the log2 normalized counts of 18 signature genes (Danaher et al. J Imm Can 2018) and pre-defined gene sets (3), respectively. Wilcoxon rank sum test was used to analyze TME GSEA between pre- and on-tx samples. Differential expression was significant if $|FC| > 1.33$, adjusted $P < 0.01$. **Results:** 19 pts were treated; all received paired biopsies. WES was adequate in 7/19 (37%) pts, with *IDH*m identified in 3/7 (43%) pts. All pts were MSI-stable, TMB: 1.01-3.57 mut/Mb. RNAseq was adequate in 7/19 (37%) pts at pre-tx and 5/19 (26%) pts at on-tx. TISS ranges trended higher for pre-tx (8.77-10.14) vs on-tx (7.36-9.51) samples. TME GSEA identified significantly enriched tumor immune infiltration ($p < 0.05$) in pre- vs on-tx samples. Differential analysis identified several gene sets related to inflammation overexpressed in pre-tx samples only, including IFN response. On-tx samples were enriched in myogenesis and coagulation gene sets. **Conclusions:** This is the first study to describe transcriptomic changes following epigenetic tx in cCS. Contradictory to our preclinical data, HDACi + DNTMi resulted in low expression of inflammation. Prior studies reported that the immune infiltrate of CS at progression is immunosuppressive; higher immune infiltrate is correlated with worse outcomes (4). Loss of inflammation may have implications for disease stability experienced by most pts on NCI 10330. Further analyses are planned to correlate TME (pro- vs anti-inflammatory infiltrates) and outcomes. Analyses are limited by small sample size, highlighting the challenges in collecting adequate CS specimens. 1. Sheikh, Schwartz et al. Mol Cancer Ther 2021. 2. Lacuna et al. ASCO 2023: #11531. 3. Bagaev et al. Can Cell 2021. 4. Richert et al. J Bone Onc 2020. Clinical trial information: NCT04340843. Research Sponsor: U.S. National Institutes of Health/National Cancer Institute - Cancer Therapy Evaluation Program; UM1CA186689; U.S. National Institutes of Health/National Cancer Institute; T32CA203703 (KL).

11527 Poster Session

Apatinib combined with ifosfamide and etoposide versus ifosfamide and etoposide in relapsed or refractory osteosarcoma (OAIE/PKUPH-sarcoma 11): A multicenter, randomized controlled trial.

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Background: Retrospective studies have suggested the potential of apatinib, an anti-angiogenesis tyrosine kinase inhibitor, plus ifosfamide and etoposide (IE) over IE in advanced osteosarcoma. This trial aimed to further compared apatinib plus IE versus IE alone in patients with advanced osteosarcomas post first-line chemotherapy failure. **Methods:** In this multi-center, randomized controlled trial, patients with histologically confirmed osteosarcoma, progressing after at least one prior line of chemotherapy, were randomized (2:1) to either apatinib plus IE or IE alone. The apatinib plus IE group received oral apatinib 500mg daily plus ifosfamide (1.8 g/m^2/d) and etoposide (100 mg/m^2/d) on days 1-3, every 3 weeks. The IE group received IE on days 1-5, every 3 weeks. Apatinib was continued until disease progression or for a maximum of one year, and IE was administered for up to 10 cycles. The primary endpoint was progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors 1.1. **Results:** A total of 81 patients were enrolled, with 53 receiving apatinib and IE, while 28 using IE alone. The median follow-up period was 9.5 (interquartile range, 7.1 to 13.0) months. The apatinib plus IE group showed a median PFS of 5.5 months (95% confidence interval [CI], 3.9 to 6.7), compared to 3.4 months (95% CI, 1.4 to 4.6) in the IE group, yielding a hazard ratio of 0.41 (95% CI, 0.24 to 0.71), P=0.0010. Objective response rates were 32.1% (95% CI, 19.9 to 46.3) for the apatinib plus IE group and 25.0% (95% CI, 10.7 to 44.9) for the IE group. Disease control rates were numerically higher in the apatinib plus IE group at 90.6% (95% CI, 79.3 to 96.9), compared to 60.7% (95% CI, 40.6 to 78.5) in the IE group. The median time to response was 1.4 months (95% CI, 1.2 to 2.6) for the apatinib plus IE group and 1.5 months (95% CI, 1.3 to 2.0) for the IE group. Duration of response also favored the apatinib plus IE group, with a median of 6.1 months (95% CI, 1.9 to 8.0) compared to 4.1 months (95% CI, 1.7 to not estimated [NE]) in the IE group. The median overall survival has not yet been reached in either group. Grade 3-4 treatment-related adverse events occurred in 69.8% of patients in the apatinib plus IE group and 64.3% in the IE group, with the most common events being white blood cell count decreased and neutrophil count decreased. **Conclusions:** Apatinib plus IE demonstrated a significant improvement in PFS in patients with advanced osteosarcomas, with an acceptable safety. Clinical trial information: NCT05277480. Research Sponsor: None.

Efficacy endpoints.

Endpoints	Apatinib+IE (n=53)	IE (n=28)
PFS, months, median, 95%CI	5.5 (3.9-6.7)	3.4 (1.4-4.6)
HR (95%CI)	0.41 (0.24, 0.71)	
P	0.0010	
ORR, n, %, 95%CI	17 (32.1) (19.9, 46.3)	7 (25.0) (10.7, 44.9)
DCR, n, %, 95%CI	48 (90.6) (79.3, 96.9)	17 (60.7) (40.6, 78.5)
TTR, months, median, 95%CI	1.4 (1.2-2.6)	1.5 (1.3-2.0)
DOR, months, median, 95%CI	6.1 (1.9-8.0)	4.1 (1.7-NE)

11528 Poster Session

Efficacy and safety of fruquintinib-based treatment in patients with refractory bone and soft tissue sarcomas after developing resistance to several TKIs: A multi-centered retrospective study.

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Background: Multi-targeted tyrosine kinase inhibitors (TKIs) have been approved as the second-line therapy for refractory bone and soft tissue sarcomas, prolonging progression-free survival (PFS) but with still limited duration of disease control. Fruquintinib is a highly selective TKI that inhibits vascular endothelial growth factor receptor (VEGFR)-1,2,3 without undergoing metabolism by liver enzymes. This retrospective study assessed the efficacy and safety of fruquintinib-based treatment in refractory bone and soft tissue sarcomas after multiple lines of TKIs. **Methods:** This study included patients with refractory bone and soft tissue sarcomas, who had developed several lines of resistance to TKIs and then received fruquintinib-based treatment from November 2021 to August 2023. The primary endpoint was the PFS rate at 4 months (4m-PFSR). Secondary endpoints included PFS, overall survival (OS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs). **Results:** We included 124 patients from two Chinese centers: 56 (45.2%) osteosarcoma, 28 (22.6%) Ewing sarcoma, 7 (5.6%) chondrosarcoma, and 33 (26.6%) soft tissue sarcomas. Among them, 72 (58.1%) patients had target lesions limited to the lung and bone. The median age was 21 (interquartile range [IQR], 12-39) years. Seventy-three (58.8%) patients previously had four or more lines of therapy. All patients had received TKI treatment, and among them, 19 (15.3%) had used more than two lines of TKIs. During fruquintinib treatment, 18 (14.5%) patients received monotherapy, 34 (27.4%) combined with albumin-bound paclitaxel, 31 (25.0%) combined with irinotecan or topotecan, and 15 (12.1%) combined with programmed cell death 1/programmed cell death-ligand 1 (PD1/PD-L1) inhibitors. With a median follow-up time of 6.8 (IQR, 4.6-9.4) months, 22 (17.7%) patients had partial response (PR) and 78 (62.9%) were in stable disease (SD). The 4m-PFSR was 58.4% (95% confidence interval [CI], 49.6%-67.1%). The median PFS and OS were 4.4(95% CI, 3.9-5.0) months and 11.4(95% CI, 10.3-12.5) months. In multivariate analysis, a high hazard ratio (HR) of 1.79 (95% CI, 1.10-2.93; P=0.020) for progression or death was associated with target lesions located outside lung and bone. 88 AEs were recorded in 47(37.9%) patients and the most common were pneumothorax (18/124, 14.5%), diarrhea (8/124, 6.5%), mucositis oral (7/124, 5.6%), and thrombocytopenia (7/124, 5.6%). **Conclusions:** Fruquintinib demonstrated as an potential option for patients with refractory bone and soft tissue sarcomas after developing resistance to several TKIs, with satisfactory efficacy and safety profile when used in combination therapy. More prospective trials on fruquintinib are needed, especially on different pathological types and diverse combination regimens. Clinical trial information: NCT06202599. Research Sponsor: None.

11529 Poster Session

Updated results from ALTER-S002: A single-arm multicenter trial of the combination of anlotinib with chemotherapy in patients with stage IIB classic osteosarcoma of the extremity.

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Background: The overexpression of multiple tyrosine kinase receptors in osteosarcoma indicated a promising therapy targeting these receptors. Anlotinib is a multi-targeted tyrosine kinase inhibitor that potentially inhibits tumor angiogenesis. The combination of anti-angiogenic drugs with chemotherapeutic agents is proposed to act synergistically to achieve favorable tumor control, especially as the neoadjuvant therapy. We had reported the neoadjuvant therapy data of anlotinib in combination with chemotherapy for treatment-naive stage IIB classical osteosarcoma of the extremity in the 2023 ESMO congress. Here we report an update on the effectiveness and safety of the follow-up. **Methods:** In this open-label, single-arm, multicenter phase II clinical trial. Eligible patients(pts) were aged 12-40 years with histologically confirmed primary localized extremity classic osteosarcoma, stage IIB, operable. Pts received anlotinib (10mg, po, d1-14, q3w), doxorubicin (A) (20-25mg/m^2 iv, d1-3, q3w) and cisplatin (P) (70-90mg/m^2, iv, d1, q3w) for the first nine weeks. Pts underwent radical surgery after the exclusion of contraindications at week 10. After surgery, pts received A+P at weeks 12-14, and anlotinib plus A+P at weeks 15-20 with the drug dose unchanged. Since week 21, anlotinib (12mg, po, d1-14, q3w) monotherapy was maintained until week 104 or the occurrence of an EFS event. The primary endpoint was 24-month EFS rate, secondary endpoints were 36-month EFS rate, local recurrence rate, lung metastasis rate, 3-year OS rate and safety. **Results:** From May 2020 to Apr 2022, 52 eligible pts were enrolled, while 51 pts underwent surgery after 3 cycles of neoadjuvant therapy. At the data cut-off date (Oct. 2023), the median EFS was not reached, 12 and 24-month EFS rates were 84.18% (95% CI :70.82, 91.77) and 73.43% (95% CI :57.40, 84.21), respectively. The stratified analysis of EFS showed that the length and diameter of the target lesion are independent prognostic factors. The median OS was not reached, the 24-month OS rate was 95.92% (95% CI :84.65, 98.96). Among the 51 pts who underwent surgical treatment, 12(23.53%, 95% CI: 12.79, 37.49) pts experienced recurrence or metastasis. Most treatment-related adverse events (TRAEs) were grade 1-2. Grade 3/4 TRAEs (≥20%) included neutropenia (51.92%), leukopenia (38.46%), thrombocytopenia (36.54%) and anemia (32.69%). **Conclusions:** The updated results suggested that anlotinib combined with doxorubicin and cisplatin in the perioperative period showed favorable efficiency and manageable adverse events in Stage IIB classic osteosarcoma of the extremity. Clinical trial information: ChiCTR 2000033298. Research Sponsor: None.

11530 Poster Session

Phase II study in pediatric and AYA patients with non-metastatic high-grade extremity osteosarcoma with a risk-adapted strategy based on P-glycoprotein (ISG/OS-2): A correlative study on tumour immune microenvironment.

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Background: According to retrospective osteosarcoma series, P-glycoprotein (Pgp) overexpression predicts for poor outcome. A risk-adapted treatment strategy, the ISG/OS-2 trial, evaluated the use of mifamurtide, an EMA-approved innate immunity-modulator, in Pgp-positive patients (pts) (NCT01459484). Here, we present a correlative study to develop a predictive classifier based on tumour immune microenvironment gene profiling. **Methods:** 62 localized osteosarcoma pts were enrolled at diagnosis. RNA was extracted from pre-treatment FFPE and non-decalcified tissues and was analyzed by PanCancer Immune profiling panel (NanoString Technologies, Seattle, WA, US), including 730 immune genes. 33/62 pts (53%) were Pgp-positive and underwent chemotherapy (CT) and adjuvant mifamurtide, Pgp-negative received CT alone. Univariate Cox regression analysis and pts stratification with the MaxStat package were performed. Receiver operating characteristic (ROC) curve analysis to evaluate the model performance and validation in 2 independent sets were applied. Primary objective was the identification of prognostic signatures of osteosarcoma pts at diagnosis and in pts undergoing mifamurtide. **Results:** No significant differences in terms of overall survival (OS) and event-free survival (EFS) were shown between Pgp-positive and Pgp-negative pts. Therefore, tumour immune gene expression profiles of all 62 pts were analyzed, irrespective of treatment. First, we identified a 21-gene OS-signature able to stratify all pts into high- and low-risk: 5-year OS for high-risk pts 35.7%, and 89% for the low-risk ($p < 0.0001$, AUC 0.865). The OS-signature was validated in two independent pts cohorts: GSE16091 (n=34) and GSE33383 (n=87) from the Gene Expression Omnibus (GEO) and significantly distinguished in both cohorts high- and low-risk pts ($p < 0.0001$) - despite in the validations sets different molecular platforms (Affymetrix Human Genome U133A Array and Illumina Human-6 v2.0, respectively) were used. Next, we identified a 31-gene EFS signature, with a 5-year EFS of 32.2% for high-risk and 93% for low-risk pts ($p < 0.05$, AUC = 0.872). Finally, we focused on the subgroup of pts Pgp-positive, treated with CT+mifamurtide: a 54-gene signature able to discriminate high-risk pts, 5-year EFS of 0%, and low-risk pts, 5-year EFS of 100%, was identified ($p < 0.05$, AUC 0.964). A tumor microenvironment deconvolution analysis is ongoing. **Conclusions:** Tumour immune microenvironment prognostic gene signatures have been identified for risk stratification of pts with osteosarcoma, regardless of treatment with mifamurtide. Importantly, we have developed a mifamurtide-specific signature that predicts EFS. This promising tool might be used to select pts who could benefit from adjuvant mifamurtide. Clinical trial information: NCT03737435. Research Sponsor: CARISBO Foundation; Alliance Against The Cancer (ACC).

11531 Poster Session

Anti-angiogenic TKIs in patients with advanced Ewing sarcoma: A systematic review and single-arm meta-analysis.

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Background: The treatment of patients with localized Ewing Sarcoma (ES) is well established; however, strategies for relapsed disease remain uncertain. Encouraging outcomes have surfaced from early-phase trials assessing tyrosine kinase inhibitors (TKIs) with anti-angiogenic properties in this population. Hence, we conducted a systematic review and meta-analysis to synthesize current data on efficacy and safety of TKIs in patients with ES. **Methods:** We comprehensively searched PubMed, Embase, and Cochrane databases for clinical trials and cohort studies assessing anti-angiogenic TKIs in the treatment of advanced ES patients who had received at least one previous line of therapy. Main outcomes were objective response rate (ORR), disease control rate (DCR), median progression-free survival (PFS), and safety. Heterogeneity was assessed using I^2 statistics. All analyses were conducted using R software (v.4.2.2), employing random effects models. **Results:** We included 10 studies: four phase II clinical trials and six retrospective cohort studies, comprising 191 patients. The following TKIs were evaluated: cabozantinib, regorafenib, apatinib, anlotinib and sorafenib. Median age in each study varied from 15 to 33 years, and 48.6% of patients had received ≥2 previous lines of therapy. In a pooled analysis of all ES patients treated with TKIs, the ORR was 30.1% (95%IC 16.3-43.8; I^2=83.14%) and DCR was 66.8% (95%IC 59.4-73.5; I^2=3.97%). In a comparative analysis stratified by drug, anlotinib was associated with an increased ORR ($p<0.01$) and no difference was seen in DCR among TKIs assessed (p=0.26). Seven studies evaluated TKIs in monotherapy, while the others included patients treated with TKIs + chemotherapy (CT); TKI+CT displayed higher ORR (p=0.04) and DCR (p=0.05), in a subgroup analysis by treatment strategies. The median PFS varied from 3.5 to 16.0 between drugs, and the overall median PFS was 4.4 months (95%CI 3.4-10). Dose reduction and interruption of treatment due to toxicity were reported in 39.6% and 6% of patients, respectively. Most common grade 3 or 4 adverse events were leukopenia (24.5%), anemia (8.8%), hypertension (5.6%), and diarrhea (4.3%). **Conclusions:** Anti-angiogenic TKIs are well tolerated and have shown anti-tumoral activity and clinical benefit in the treatment of patients with advanced Ewing sarcoma. Prospective randomized trials with adequate control groups are warranted to further evaluate the benefits of these agents. Research Sponsor: None.

TKI	N	ORR (95%CI)	DCR (95%CI)	Median PFS (95% CI), Months
Cabozantinib	60	23.3% (14.3 - 35.6%)	65.0% (52.2 - 75.9%)	4.4 (3.4 – 5.7)
Regorafenib	53	11.3% (5.2 - 23.0%)	58.5% (44.9 - 70.9%)	3.5 (2.6 – 3.5)
Anlotinib	44	63.6% (48.6 - 76.4%)	75.0% (60.3 - 85.6%)	10.0 (6.7 – 10)
Apatinib	20	30.0% (14.1 - 52.7%)	75.0% (52.2 - 89.2%)	16.0 (2.2 – NE)
Sorafenib	14	14.3% (3.6 - 42.7%)	78.6% (50.6 - 92.9%)	NA
All TKIs	191	30.1% (16.3 - 43.8%)	66.8% (59.4 - 73.5%)	4.4 (3.4 - 10)

11532 Poster Session

Novel models for the functional characterization of SDHA germline variants to predict cancer risk.

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Background: SDHA mutations are the most common cause of SDH-deficient GIST. More than 80% of SDHA-mutant GIST are associated with heterozygous germline mutations. Enhanced cancer surveillance of individuals carrying a known pathogenic germline SDHA mutation has the potential to detect early-stage tumors, allowing for curative surgery. However, of the > 1000 SDHA missense variants listed in ClinVar, > 95% are VUS. We must improve our ability to interpret the significance of SDHA variants before genetic sequencing can be utilized to its fullest potential for assessing cancer risk. **Methods:** We generated a novel clonal *SDHA* knock out ($SDHA^{KO}$) human cell line with complete loss of SDHA expression and enzymatic activity. We next generated a clonal cell line harboring one copy of a landing pad cassette, allowing for site-specific integration of transfected expression cassettes mediated by Bxb1 recombinase. We validated that wild-type *SDHA* cDNA restored SDHA expression and enzymatic activity to levels equivalent to the parental HAP1 cells. We then selected 17 known benign variants (B,LB) and 21 known cancer missense variants (P, LP). In addition, we selected six missense variants associated with primary mitochondrial disease rather than cancer. Lastly, we selected 22 missense VUS. We created a mutant cell line in our KO landing pad cell line for each SDHA variant, as well as a control nonsense variant ($SDHA^{R31X}$). Cell lines were analyzed for normalized SDH activity measurements ($SDHA^{WT}$ activity score = 1) **Results:** As expected, benign variants were collectively WT-like, with a mean Activity Score of 0.917. However, there was substantial variability amongst individual variants, with $SDHA^{Y55H}$ having the lowest score at 0.215. Although known PMD variants (mean Activity Score = 0.358) were associated with lower functionality than that of benign variants, the extent of SDH dysfunction corresponding to cancer variants (mean Activity Score = 0.007) was substantially lower. Notably, all but one cancer variant could be described as functionally amorphic, as their Activity Scores were not significantly different from that of a control null variant, $SDHA^{R31X}$, whose mean Activity Score was 0.004. We used the Activity Scores of these clinical control variants to establish thresholds to classify "cancer-like" or "benign-like" variants, which meet ACMG/AMP criteria for PS3_strong and BS_3 strong evidence according to an OddsPath calculation. We biochemically profiled 22 cell lines expressing a SDHA VUS. Using functional data and ACMG criteria, 3 variants could be reclassified as "Likely Benign", 14 could be reclassified as "Likely Pathogenic", and 5 remained a VUS (77% successfully reclassified). **Conclusions:** Functional characterization of SDHA germline missense variants has the potential to identify individuals who will benefit from genetic counseling and enhanced cancer screening procedures. Research Sponsor: None.

11533 Poster Session

Peak part 1 summary: A phase 3, randomized, open-label multicenter clinical study of bezuclastinib (CGT9486) and sunitinib combination versus sunitinib in patients with gastrointestinal stromal tumors (GIST).

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Background: After initial response to first line therapy with imatinib, GISTs commonly progress due to secondary resistance mutations in KIT. As the KIT mutation targeting profiles of bezuclastinib (type I TKI) and sunitinib are distinct, when combined they inhibit a broad spectrum of secondary KIT mutations. Herein we report extended experience of patients treated with 2nd line combination bezuclastinib and sunitinib, including response assessment and safety. **Methods:** Peak (NCT05208047), a global randomized Phase 3, open-label study, aims to evaluate efficacy and safety of bezuclastinib + sunitinib vs sunitinib in GIST pts with imatinib intolerance or resistance. In Part 1a of the 3-part study, the dose of an optimized formulation of bezuclastinib was escalated in serial cohorts to achieve a target exposure comparable to that achieved at the RP2D established in the prior Phase 1b/2a study. Part 1b evaluated the interaction between bezuclastinib + sunitinib. Key inclusion: adult with locally advanced, metastatic and/or unresectable GIST, ≥1 measurable lesion according to modified RECIST v1.1, and ECOG PS 0 to 2. Part 1 completed enrollment in Apr 2023. Based upon PK and safety, a dose of bezuclastinib 600 mg QD + sunitinib 37.5 mg QD was selected for Part 2. All Part 1 data reported herein are as of Aug 2023; updated safety and efficacy will be presented. **Results:** Part 1 has completed enrollment with 19 pts in Part 1a and 23 in 1b. In Part 1a, Cohort 1 included 5 pts starting at bezuclastinib 300 mg QD + sunitinib 37.5 mg QD; Cohort 2 included 14 pts at bezuclastinib 600 mg QD + sunitinib 37.5 mg QD. Pt characteristics in Part 1a+1b: median age - 60 yrs (range: 33-77); 81% men; 98% ECOG PS 0-1; 98% metastatic and 2% locally advanced. The majority of TEAEs were low grade and reversible with low rate (38%) of Grade 3+ events. There were limited (24%) dose reductions and infrequent (n=2) discontinuations due to TEAEs. Three pts experienced serious AEs possibly associated with study medications. In pts evaluable for response (received ≥1 cycle of study treatment and had assessments at baseline and post-baseline [n=40]), the objective response rate (ORR) was 20% (6 confirmed PRs, 2 unconfirmed PRs). Data remain immature to estimate median PFS for Part 1 pts. In a subset of pts with prior imatinib only (n=6), the closest approximation for pts enrolling in Part 2, the ORR was 33% (2 confirmed PRs). The majority of 2nd-line pts remain on treatment past 12 months. **Conclusions:** Data from Peak Part 1 show an encouraging safety and tolerability profile generally consistent with published sunitinib monotherapy experience. ORR in evaluable pts from Part 1 was 20%; ORR in 2nd line pts was 33%. Part 2 of the Peak study is actively enrolling pts globally at the selected dose of bezuclastinib 600 mg QD + sunitinib 37.5 mg QD versus sunitinib 37.5 mg QD. Clinical trial information: NCT05208047. Research Sponsor: Cogent Biosciences, Inc.

11534 Poster Session

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

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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 stage II-III GIST who underwent R0 surgery and following adjuvant imatinib/avapritinib were enrolled prospectively. Surgical tissue samples were collected. Blood samples were drawn pre-surgically, and at 7 days, 1 month, and every 3–6 months post-surgically. Tumor-derived variants were identified by whole-exon sequencing of the surgical tissues. Up to 50 highly ranked variants with a variant allele frequency 3.0% were selected for the personalized panel design, which was subsequently used to assess MRD status. **Results:** A total of 36 patients with a median age of 65 years were included in the current analysis (data cutoff on January 16, 2024). Most tumors (17/36, 47%) were located at the stomach or gastroesophageal junction, and 94.4% of patients (34/36) did not receive neoadjuvant treatment. The mean maximum diameter of tumors was 7.87 ± 2.87 cm. At present, 36 tissue samples, 34 pre- and 161 post-surgical blood samples were collected and analyzed. Tissue sample-based sequencing identified variants in *KIT* and *PDGFRA* in 31 (86%) and 4 (11%) patients, respectively. 98.4% (1003/1019) of tumor variants included in personalized panels were patient-specific. ctDNA was detected in 64.7% (22/34) of pre-surgical plasma samples. The ctDNA-positive rate at baseline was associated with tumor mutation burden ($p < 0.05$), rather than tumor size ($p = 0.6$). Landmark analysis at 1 week post-surgery showed that 12.1% of patients were positive for ctDNA. Up to now, 4 patients were identified with tumor recurrence based on imaging results. Among these patients, 3 patients (3/4) exhibited ctDNA positivity preceding radiological recurrence. Notably, a 71-year-old patient was ctDNA-positive at 1 week post-surgery. Longitudinal analysis revealed that his ctDNA became negative after adjuvant treatment but turned positive at 9 months post-surgery , with a lead time of 2 months prior to his radiological recurrence. Additionally, a patient tested positive for ctDNA at 3 months post-surgery but had negative imaging results. Follow-up visits are ongoing for this patient. **Conclusions:** The present study suggests that personalized tumor-informed ctDNA has the potential to inform recurrence in high-risk stage II-III GIST patients. Clinical enrollment is still ongoing. Research Sponsor: None.

11535 Poster Session

Combination targeted therapy of avapritinib and sunitinib for patients with refractory advanced gastrointestinal stromal tumors after failure of standard treatments: Early results from a multi-institutional pilot study.

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Background: The objective of this study was to explore the efficacy and safety of the combination of avapritinib and sunitinib in refractory GISTs. **Methods:** This was a multi-institutional prospective cohort study in part of a real-world trial (NCT05461664) exploring avapritinib in GIST patients (pts) after failure of standard treatments. From Jan 2022 to Sep 2023, participants were administered avapritinib at 100–200mg QD combined with sunitinib at 25–37.5mg QD continuously in 28-day cycles until PD or discontinuation. Clinical outcomes including ORR, survival and safety were assessed. **Results:** Twenty pts, generally heavily pretreated (65% with ≥4 prior TKIs, and 70% had progressed on ripretinib) were enrolled across seven participating centers. Median sum of target lesions was 27.0cm (range, 6.6–80.8). Among them, nine pts had primary *KIT 11* mutation, 10 harbored *KIT 9*and one harbored *KIT 17*. Nine pts had *KIT* activation-loop (AL) mutations without *KIT*ATP-binding pocket (ABP) mutations (*KIT*AL^{pos} ABP^{neg}), 2 had *KIT* ABP mutations without *KIT* AL mutations (*KIT*AL^{neg} ABP^{pos}). ORR was 20% (4 PR), 15 pts (75%) had SD, one (5%) had PD with a CBR (PR+SD≥16w) of 75%, assessed via mRECIST v1.1. Tumor shrinkage was observed in 18 pts (90%), with a median best percent change in target lesions of -20.2% (range, -54.5% to 16.1%). With a median follow-up duration of 11.3 months (range, 2.3–20.9), 12 pts progressed, 3 were withdrawal, 7 were dead and 5 continued to receive combination therapy. Median PFS (mPFS) was 6.6 months (95% CI 5.8-7.4). Median OS was not reached. mPFS in pts with primary *KIT 11* was similar compared to those with *KIT 9*. Regarding secondary *KIT* mutations, mPFS was numerically longer in *KIT* AL^{pos} ABP^{neg} pts compare to without (6.9 months VS 2.3 months, p=0.251). mPFS was significantly shorter in pts with *KIT*AL^{neg} ABP^{pos} than without (1.1 months VS 6.9 months, p<0.001). Three pts carrying *KIT 16 L783V* exhibited significantly longer mPFS than others (18.2 months VS 6.4 months, p=0.041). The dose of avapritinib (100–150 mg/d) and sunitinib (25–37.5 mg/d) could be tolerated. Common adverse events (AEs) were anemia, leukopenia, diarrhea, fatigue, periorbital and face oedema, and memory impairment. Common grade ≥3 AEs included leukopenia (30.0%), neutropenia (25.0%), anemia (20.0%), diarrhea (20.0%), and gastrointestinal hemorrhage (15.0%). **Conclusions:** The combination of avapritinib and sunitinib provided meaningful clinical benefit with an acceptable safety profile in pts with refractory GISTs, except for those harbored *KIT*AL^{neg} ABP^{pos} mutations. Clinical trial information: NCT05461664.
Research Sponsor: None.

Comparison of machine learning algorithms for the radiomic classification of gastric subepithelial tumors.

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Background: Diagnostic challenges arise in classifying gastric subepithelial tumors (SETs) due to the absence of specific imaging findings and limitations in endoscopic biopsy, particularly for deep-seated tumors. Differentiating SETs that require surgical intervention from those suitable for diagnostic imaging follow-up is crucial. Gastrointestinal stromal tumors (GIST), with malignant potential, necessitate prompt resection, while leiomyoma and schwannoma are benign and can be followed up if asymptomatic. Many radiomic approaches using machine learning (ML) were tried to classify gastric SET. Nevertheless, a comprehensive exploration of current ML algorithms still needs to be explored. **Methods:** The patients who underwent the surgery for gastric SET in our hospital were considered eligible subjects. All cases were confirmed by pathologic evaluation, and the cases of GIST and leiomyoma were chosen for this study. Manual segmentation and radiologist validation were performed, followed by image resampling to 1 x 1 x 1 mm resolution. Radiomics features were extracted using PyRadiomics 3.0.1, focusing on 32 first-order and shape features for interpretability and robustness. Various models, including K-nearest neighbors (KNN), support vector machines (SVM), logistic regression (LR), lightGBM, random forest (RF), and TabPFN (by Hollman N et al.), underwent evaluation. Nested cross-validation with 10 folds and 10 repetitions ensured fair comparison, and Bayesian hyperparameter optimization was conducted in a 5-fold inner CV, excluding TabPFN. Comparative evaluation included area under the receiver operating characteristics (AUROC), accuracy, balanced accuracy, and Matthew Correlation Coefficient (MCC). **Results:** Among the 359 eligible patients, resulting in 241 GISTs and 27 leiomyomas post-exclusion. We used 26 pre-isolated cases as a test set of the model. The model test results for various ML models in classifying gastric SETs are presented (Table). Notably, LR exhibited the highest accuracy (0.899), F1 score (0.950), and AUROC (0.653) compared to other models without statistical significance. **Conclusions:** Our study highlights that LR improves the accuracy of diagnosing gastric SETs. These findings contribute to refining diagnostic approaches and may optimize patient management strategies for gastric SETs. Research Sponsor: None.

Performance metrics of machine learning models for gastric subepithelial tumor classification.

Model	Accuracy	Balanced Accuracy	F1 score	MCC	AUROC
KNN	0.895±0.026	0.505±0.043	0.945±0.014	0.015±0.120	0.594±0.176
LGBM	0.891±0.028	0.509±0.057	0.942±0.016	0.026±0.156	0.620±0.179
LR	0.899±0.016	0.5	0.950±0.009	-	0.653±0.187
RF	0.894±0.026	0.513±0.055	0.944±0.015	0.040±0.172	0.614±0.184
SVM	0.899±0.017	0.500±0.002	0.947±0.009	-0.0007±0.007	0.519±0.191
TabPFN	0.899±0.016	0.5	0.947±0.009	-	0.646±0.171

11537 Poster Session

Molecular residual disease (MRD) detection using bespoke circulating tumor DNA (ctDNA) assays in localized soft tissue sarcoma (STS): A multicenter study.

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Background: Surgery and (neo)adjuvant radiotherapy (RT) are the mainstay curative treatments for localized STS. Despite treatment, up to 50% of STS patients experience metastatic relapse, and routine use of adjuvant systemic therapy (AST) remains controversial. The presence of ctDNA following curative-intent treatment of STS is a potential biomarker for MRD and may identify patients who are likely to benefit from AST. Given the genomic heterogeneity of STS, a histology-agnostic approach to ctDNA detection in this population is desirable. **Methods:** This multicentre prospective study enrolled patients with localized, high-risk (grade $\geq$ 2, size $\geq$ 5 cm) STS. Blood samples were collected at diagnosis, post-radiotherapy, post-surgery, and at serial longitudinal time points for up to 2 years. Standard radiologic follow-up was performed concurrently. Whole exome sequencing of tumor tissue was carried out to identify patient-specific, single nucleotide variants. Personalized, and tumor-informed multiplex PCR next-generation sequencing-based ctDNA (Signatera) assays were used to track ctDNA in serial plasma samples. The primary endpoint was ctDNA detection rate of >70% at diagnosis. Secondary endpoints were MRD detection after local therapy and correlation of ctDNA detection with disease relapse. **Results:** A total of 76 subjects (female n = 43; median age [range]: 58 [21- 84] years) were included in this study from Princess Margaret Cancer Center, Stanford University, and Emory University. The most common STS types observed were leiomyosarcoma (LMS, n = 28), liposarcoma (n = 14), (predominantly dedifferentiated [n = 6]), and myxofibrosarcoma (n = 11). Among 38 pts who had blood samples collected at baseline (time of surgery), ctDNA was positive in 30/38 (79%). A baseline sample prior to radiotherapy was collected in 24 pts. Following neoadjuvant radiotherapy, 8/24 pts (33%) who were ctDNA positive at baseline became ctDNA negative, while 29/30 became ctDNA-negative after surgical resection. Median follow-up was 19 months, and 19/76 pts (25%) experienced disease recurrence Among these 19 pts, ctDNA was detected in all pts with baseline studies. ctDNA was detected at or before radiologic recurrence in 9/19 pts (47%), predominantly LMS 4/9, with a median lead time of 64.8 days (range: 0-197 days). ctDNA was detected in 14/38 patients at baseline with no radiological recurrence during follow-up period. **Conclusions:** Personalized, tumor-informed ctDNA assays can detect MRD and has prognostic value after definitive therapy, surgery and (neo)adjuvant radiotherapy, in localized STS patients. Additional studies are ongoing to evaluate ctDNA as a predictive biomarker for benefit from AST in STS. Clinical trial information: NCT03818412. Research Sponsor: University Health Network.

11538 Poster Session

AlphaMissense performance as a classifier of germline and somatic variants of unknown significance in high-grade sarcoma.

Andrew Bassim Bassim Hassan, Rachael Wilkinson, Stuart Brown, Richard Wallbank, Mirvat Surakhy, Sofia Alves-Vasconcelos, Paul Metz, Qinan Qian, Hannah Mallon, Tanya Ren, Isabel Karia, Harriet Branford-White; University of Oxford, Oxford, United Kingdom; Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

Background: Missense variants associated with high frequency, clinical context, splicing, penetrance and biochemical function are scored as pathogenic by ClinVar/ACMG (scores >99%/>90%). Pathogenic scores that range from this cut-point to 10% (benign) are referred to as variants of unknown significance (VUS). Alphafold2 is a deep neural network algorithm for protein structure trained on known molecular structures. It has informed AlphaMissense (AM) where the impact of every possible single missense variant in the human genome is assessed. The AM continuous pathogenicity score (roughly 0-0.35 benign, 0.36-0.55 ambiguous, 0.56-1.0 pathogenic) are claimed to have 90% accuracy based on ClinVar (based on 1,263 pathogenic and 1,263 benign variants). **Methods:** Here, we identified VUSs from the Oxford Sarcoma Precision Oncology real world cohort. This included the identification of somatic variants from FoundationOne Heme Sarcoma analysis of Formalin-Fixed Paraffin Embedded (FFPE) tumour samples. Germline variants were identified from whole exome sequencing (WES) (97 genes) from patient blood samples followed by analysis using GATK guidelines. All VUS identified were further analysed using AM. **Results:** AM reclassified the identified >1000 VUSs from 60 high grade sarcoma gene panels predominantly into benign or pathogenic, with only ~1% remaining as ambiguous. Variants reclassified as pathogenic were assessed for likelihood of pathogenicity based on scientific rationale. This involved evaluating current literature on the variant, determining evolutionary consensus of the residue, structural analysis to assess the potential function of the residue and enrichment of the variant within sarcoma patients compared to known frequencies across the population. **Conclusions:** In conclusion, the AM classifier dichotomises VUS to either benign or pathogenic, but this is not based on either structural or functional predictions directly. We conclude that it should not be currently used in the analysis of clinical samples seeking actionable variants but could instead stratify potential pathogenic variants for functional investigation. Research Sponsor: Hoffman La Roche.

11539 Poster Session

Phase II study to evaluate surufatinib in patients with osteosarcoma and soft tissue sarcoma that has failed standard chemotherapy: Updated analysis.

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Background: In this single-arm, open-label, multi-center, phase II study (NCT05106777) primary analysis, surufatinib (a multi-targeted, small-molecule inhibitor of VEGFR-1, 2, 3, FGFR-1 and CSF-1R) demonstrated some clinical activities for osteosarcoma and soft tissue sarcoma (STS) patients (pts) who have failed in standard chemotherapy at the 2023 ASCO (e23540). Herein, we reported the updated efficacy and safety data with more enrolled pts. **Methods:** Pts aged 14-70 years (pts ≤ 18 years have a body surface area of ≥1.5m^2) with advanced, unresectable or metastatic osteosarcoma and STS who failed or intolerance to standard chemotherapy, ECOG PS 0-1, RECIST 1.1 measurable lesion were enrolled. A Simon optimal 2-stage design was used. If ≥ 3/13 had no disease progression at 12 weeks in stage 1, the study would proceed to stage 2, and ≥ 12/43 achieved the primary endpoint, the study would be successful. Enrolled pts received surufatinib 300 mg, QD, PO in a 21-days cycle. Primary endpoint was progression-free rate at 12 weeks ($PFR_{12weeks}$). Secondary endpoints were PFS, ORR, DCR, OS and safety. **Results:** As of 31 Dec, 2023, 43 pts (median age, 48 years [range, 22-68]) were included. 51% were male and 70% had ECOG PS 1. 46.5% received ≥ 2 lines of prior therapy (range, 2-7). The main tumor histologic subtypes included 11 leiomyosarcoma (LMS), 8 liposarcoma (LPS), 4 synovial sarcoma (SS), 4 fibrosarcoma (FS) and others. Among the 41 evaluable pts, 21 pts had no disease progression at 12 weeks and $PFR_{12weeks}$ was 51.22%. ORR in 21 pts who received surufatinib as 2L therapy was 19.05% (1 CR, 3 PR). DCRs of 2L or 3L and later-line therapy were 90.48% (19/21) and 80% (16/20). The ORRs of main subtypes were 20% (2/10) in LMS and 12.5% (1/8) in LPS, respectively. After median follow up of 9.92mo, the median PFS was 5.68mo (95%CI, 4.27-12.68) for 2L pts, while 2.74mo (95%CI, 2.63-3.12) for 3L and later-line therapy pts. In main subtypes, the PFS was 7.13mo (95%CI, 2.76-NA) for LMS and 3.78mo (95%CI, 2.73-9.99) for LPS. Compared with pts who received anlotinib in prior therapy, pts without anlotinib showed longer PFS (3.07mo vs 4.27mo, p=0.1215). Treatment related adverse events (TRAEs) were mostly mild (grade 1-2), the most common including proteinuria (75%), hypertension (60%), hypertriglyceridemia (60%), diarrhea (40%), hyperbilirubinemia (40%) and urine occult blood (40%). Grade 3-4 TRAEs were recorded in 16 pts including hypertension, proteinuria, hypertriglyceridemia, hyperbilirubinemia. **Conclusions:** The updated results continued to support the clinical activity of surufatinib as second-line therapy in advanced osteosarcoma and STS who failed in standard chemotherapy with long-term follow-up, while the safety profile remained satisfactory, especially for LMS pts. Surufatinib might be a potential second-line option for pts with advanced osteosarcoma and soft tissue sarcoma. Clinical trial information: NCT05106777. Research Sponsor: None.

11540 Poster Session

Treatment of patients with dedifferentiated liposarcoma (DDLPS) with the MDM2–p53 antagonist brigimadlin and p53 function: A longitudinal analysis of circulating microRNAs (miRNAs) in a first-in-human phase Ia/Ib study.

Alexander Peltzer, Patricia LoRusso, Mrinal M. Gounder, Noboru Yamamoto, Neeta Somaiah, Iwona A. Lugowska, Victor Moreno, Michael Teufel, Girish Jayadeva, Raphael Hesse, Gregor Sturm, Patrick Schöffski; Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an Der Riss, Germany; Yale University School of Medicine, Yale Cancer Center, New Haven, CT; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical Center, New York, NY; National Cancer Center Hospital, Tokyo, Japan; The University of Texas MD Anderson Cancer Center, Houston, TX; Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; START Madrid, Hospital Fundación Jiménez Díaz, Madrid, Spain; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; University Hospitals Leuven, Department of General Medical Oncology, Leuven Cancer Institute, Leuven, Belgium

Background: The tumor suppressor and transcription factor p53 mainly exerts its function through transcriptional regulation of many target genes, including those involved in the biogenesis of some miRNAs. Brigimadlin (BI 907828) is a highly potent, oral MDM2–p53 antagonist under investigation in an ongoing Phase Ia/b study (NCT03449381) in patients with advanced solid tumors, including DDLPS. Here, we present data from a longitudinal analysis of miRNAs isolated from the plasma of patients with advanced DDLPS treated with brigimadlin in the Phase Ib part of the study. The aim of this analysis was to identify whether baseline miRNA expression and/or longitudinal changes in miRNA may be associated with response to brigimadlin in patients with DDLPS or used as surrogate pharmacodynamic markers. **Methods:** In Phase Ib, patients received brigimadlin once every 3 weeks; all patients had *MDM2*-amplified, *TP53* wild-type disease. Plasma samples for miRNA analysis were taken longitudinally from patients at baseline and every cycle until the time of the last available sample (LAS). miRNA was purified from plasma and analysed using miRNA-specific next-generation sequencing (NGS; Qiagen QiaSeq on an Illumina NovaSeq sequencer) to identify changes in miRNA expression that may be relevant to describe the mode of action of brigimadlin. Samples with fewer than 200 detected miRNAs were excluded. Analyzed samples contained at least 1% miRNA as a percentage of total RNA content, established as a cut-off on other plasma evaluation samples. Differential miRNA analysis was performed using a linear model; additional predictive analysis was performed with a Cox hazard ratio model. **Results:** Plasma samples for miRNA analysis were available from 51 patients with DDLPS. For this analysis, baseline plasma samples were available from 26 patients, and samples collected at Cycle 3 or LAS were available from 24 patients. Differential expression analysis revealed that several cancer-related miRNAs, known to regulate p53/p53-related mRNAs, were significantly downregulated upon brigimadlin treatment compared to baseline; specifically, levels of hsa-miR-6131, hsa-miR-92b-3p, hsa-miR-490-5p, hsa-miR-5004-3p, and hsa-miR-548ar-5p were all downregulated. Baseline miRNA profiles that correlated with time on treatment and efficacy of brigimadlin will be presented. **Conclusions:** We present a comprehensive assessment of a longitudinal miRNA analysis by NGS from samples collected from patients treated with the MDM2–p53 antagonist brigimadlin. These data suggest that restoration of p53 function by brigimadlin may be achieved in patients with DDLPS. A further deconvolution of the analysis results with additional data is underway. Clinical trial information: NCT03449381. Research Sponsor: Boehringer Ingelheim.

11541 Poster Session

Proteomic analysis in patients with dedifferentiated liposarcoma (DDLPS) in a phase Ia/Ib study of the MDM2–p53 antagonist brigimadlin.

Yarúa Jaimes, Patricia LoRusso, Gregor Sturm, Mrinal M. Gounder, Noboru Yamamoto, Neeta Somaiah, Iwona A. Lugowska, Victor Moreno, Alexander Peltzer, Michael Teufel, Girish Jayadeva, Patrick Schöffski; Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine & Clinical Pharmacology, Biberach an Der Riss, Germany; Yale University School of Medicine, Yale Cancer Center, New Haven, CT; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical Center, New York, NY; Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; The University of Texas MD Anderson Cancer Center, Houston, TX; Early Phase Clinical Trials Department, Maria Skłodowska-Curie National Research Institute and Oncology Centre, Warsaw, Poland; START Madrid, Hospital Fundación Jiménez Díaz, Madrid, Spain; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; University Hospitals Leuven, Department of General Medical Oncology, Leuven Cancer Institute, Leuven, Belgium

Background: The tumor suppressor p53 primarily exerts its suppressive function via the transcriptional regulation of target genes. Both preclinical and clinical studies have demonstrated that restoring p53 activity elevates GDF-15, a p53 target, in plasma; however, the effects of other circulating proteins are not well understood. Brigimadlin (BI 907828), a highly potent, oral MDM2–p53 antagonist, is being investigated in an ongoing Phase Ia/Ib study (NCT03449381) in patients with advanced solid tumors, including DDLPS. To understand the effects of brigimadlin on the circulating proteome, we present data from a longitudinal proteomic analysis of plasma samples from patients with DDLPS who received brigimadlin every 3 weeks in Phase Ib. **Methods:** The Human DiscoveryMAP assay (Rules-Based Medicine) was used for protein analysis, measuring levels of 204 proteins with the Luminex platform. Plasma samples, collected at baseline and Cycle 3 Day 1 (C3 D1), were used for differential protein expression using a linear model. Proteins that showed a significant differential expression between cycles were further explored by incorporating additional covariates (time on treatment, best overall response, overall survival) into a Cox hazards ratio model. **Results:** Baseline and C3 D1 plasma samples were available from 37 patients with DDLPS. At baseline, angiopoietin-1, C-C motif chemokine 16, PAI-1, and C-C motif chemokine 5 were higher in DDLPS samples than in other tumor samples (samples from 24 patients in the same study), whereas levels of gamma enolase were lower in DDLPS samples. After patients with DDLPS were treated with brigimadlin (C3 D1), there were significant changes vs baseline in the expression of several proteins (i.e., up- or downregulation), including angiopoietin-1 (down, $p = 0.02$), LAP_TGF-beta (down, $p = 0.02$), PAI-1 (down, $p = 0.085$), thrombomodulin (down, $p = 0.062$), and serpinA7 (up, $p = 0.031$). Levels of AXL receptor tyrosine kinase (UFO) were downregulated in patients who achieved a CR or PR ($n = 11$; $p = 0.0092$) or SD ($n = 23$; $p = 0.03$), according to RECIST. However, in patients with PD ($n = 3$), baseline UFO levels were higher vs patients achieving CR/PR (mean baseline $\log_2$ expression: 3.6 μg/L vs 3.0 μg/L, respectively) and were not downregulated during treatment. Correlation of changes in thrombomodulin and neutrophil gelatinase-associated lipocalin levels with myelosuppressive events will be shown. **Conclusions:** These findings provide insight into the proteomic changes associated with brigimadlin treatment in patients with DDLPS and highlight potential biomarkers for treatment response and adverse events. Further investigation is needed to determine their significance and impact on patient outcomes. Clinical trial information: NCT03449381. Research Sponsor: Boehringer Ingelheim.

11542 Poster Session

Molecular characterization of long-term and short-term survivors of metastatic uterine leiomyosarcoma.

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Background: While some metastatic uterine leiomyosarcomas (uLMS) are clinically aggressive, others have a more indolent disease pace, suggesting biologic heterogeneity. Our objective was to determine whether the molecular characteristics of metastatic uLMS tumors differed between long-term survivors (LS) and short-term survivors (SS). **Methods:** Patients with metastatic uLMS between 1/1/2000 – 11/31/2020 who received care at our institution and had tumor tissue available were included. uLMSs were subjected to a targeted DNA next-generation sequencing panel of up to 505 cancer-related genes. Metastatic overall survival (mOS) was calculated from the date of diagnosis of metastatic disease until the date of death or last follow-up. LS was defined as mOS >2 years and SS as mOS <2 years. Appropriate statistical tests were used. **Results:** Our cohort included 17 LS and 10 SS (Table). uLMSs from LS harbored *TP53* alterations in 58% of cases compared to 90% of SS (P<0.001). Rate of *RB1* alterations in LS was 76% compared to 50% in SS (P<0.001). Rates of somatic genetic alterations affecting *ATRX*(11% LS vs. 20% SS) and *BRCA2*(47% LS vs. 50% SS) were similar between groups (P>0.05 for both). Most *BRCA2*alterations (92%) were homozygous deletions. Levels of chromosomal instability as quantified by the fraction of genome altered was similar between groups (median 27.3% in LS versus 22.9% in SS, p=0.26). Tumor mutational burden was low in both groups. **Conclusions:** While uLMS from LS and SS have similar levels of chromosomal instability and tumor mutational burden, uLMS in LS have lower rates of *TP53* alterations compared to SS patients, as well as compared to previously reported rates in uLMS. Rates of *RB1*alterations were higher in LS compared to SS. Interestingly, the rate of *BRCA2*alterations in both LS and SS is higher than previously reported and provides rationale for next-generation sequencing in patients with metastatic uLMS. Further studies in larger cohorts to validate these findings are warranted. Research Sponsor: Memorial Sloan Kettering Cancer Center.

Clinical characteristics of the cohorts.

	Long Survivors (n=17)	Short Survivors (n=10)
Median Age at Diagnosis of Metastatic Disease, years (range)	54 (30-74)	55 (30-71)
Metastatic Sites at Time of First Metastatic Disease, n (%)		
1	6 (35)	0
≥2	11 (65)	10 (100)
Recurrences, n (%)		
Single	3 (18)	0
Multiple	14 (82)	10 (100)
Deaths, n (%)	0	10 (100)
Median follow-up time, months (range)	100 (47-171)	13 (2-16)

11543 Poster Session

Predictive gene signature for trabectedin efficacy in advanced soft-tissue sarcoma: A Spanish group for research in sarcoma (GEIS) study.

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Background: Predictive biomarkers of trabectedin represent a clinical unmet need to support the rational selection of this drug in the advanced soft-tissue sarcomas (STS) setting. A few potential predictive biomarkers of trabectedin had been described in previous studies, including *ERCC1*, *BRCA1*, and *HMGA1*, among others; however, they are based mostly on the analysis of single selected molecular factors. We presented here a predictive transcriptomic-based signature for trabectedin efficacy in STS. **Methods:** A total of 140 patients with advanced STS (at diagnosis or at any time from then on), with paraffin tumor block available, with at least 2 lines of treatment in advanced disease (one of them trabectedin) were included in this study. Gene expression was evaluated by direct transcriptomics, using HTG EdgeSeq Oncology Biomarkers Panel (HTG Molecular Diagnostics, Inc.; Tucson, AZ, USA). Raw counts were normalized to transcripts per million (TPM). Univariate Cox regression analysis was performed to find genes significantly associated with PFS and only those genes with significantly different curves were further retained ($P < 0.05$). These remaining genes were used as input to build a gene expression signature, using a multivariate Cox regression applying a Lasso penalty. Risk scores were calculated by multiplying the expression of every gene with its corresponding Cox regression coefficient. **Results:** A series of 140 patients was studied, with a median age of 51, 54% males, and a median follow-up from diagnostics of 45 months. The most frequent subtypes were L-sarcomas (54%). A twenty-nine-gene predictive signature of trabectedin efficacy was built for advanced STS treatment. This signature included 13 and 16 genes associated with resistance or sensitivity to trabectedin, respectively. Genes associated with low efficacy of trabectedin included *HMGA1*, *NES*, *FANCA,* and *FANCB*, among others, whereas the high expression of genes such as *NTRK2* or *CDKN2A*were associated with higher activity of trabectedin. Patients in the high-risk gene signature group showed a significantly worse PFS compared with patients in the low-risk group: [2.0 months (95% CI 1.7-2.2) vs. 8.2 months (95% CI 5.1-11.3), $p<0.001$]. **Conclusions:** Our study identified a new 29-gene-based signature that significantly predicts trabectedin efficacy in STS patients. Prospective validation of this predictive gene signature is warranted. Research Sponsor: Spanish Group for Research in Sarcomas (GEIS).

11544 Poster Session

Characterizing patterns of mTORC1 activation across sarcoma subtypes using single-sample gene set enrichment analysis (ssGSEA) and a national biomarker database.

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Background: The mTOR pathway is a central signaling circuit that contributes to cancer cell proliferation, angiogenesis, metabolism, and other pivotal processes. The phase III SUCCEED trial showed marginal benefit of mTOR inhibition (mTORi) in chemo-responsive sarcomas, despite promising foundational phase II data. Since these trials did not account for mTOR-related physiology, we sought to identify sarcoma subgroups that display mTORC1 activated/activation phenotypes (mTORC1-act) that might derive more benefit from mTORi. **Methods:** DNA (592-gene or whole exome; N=7028) and RNA (whole transcriptome; N=3757) sequencing was performed from sarcoma patient samples, representing 49 histologic subtypes, submitted to Caris Life Sciences (Phoenix, AZ). A transcriptomic signature associated with up-regulation of mTORC1 complex activity (HALLMARK_MTORC1_SIGNALING, mSigDB) was analyzed by single-sample Gene Set Enrichment Analysis (ssGSEA). Real-world overall survival (OS) was obtained from insurance claims data and calculated from date of biopsy to last contact, with hazard ratio calculated using Cox proportional hazards model (p-values calculated by log-rank test). **Results:** Among the most mTORC1-act subtypes were PEComa (n=49, median ssGSEA score=0.114) and osteosarcoma (n=163, median score=0.084). Novel findings included high degrees of mTORC1-act in UPS (n=225, median score=0.132), IMT (n=36, median score=0.167), and epithelioid sarcoma (n=26, median score=0.155). Histologic subtype was a strong predictor of mTORC1-act ($p<0.00001$); other predictors were alterations in *TSC2* ($p<0.0001$), *TSC1* (p=0.0019), *PTEN* (p=0.0126), and *PIK3R1* (p=0.0223). In PEComa, *TSC2* alterations were associated with mTORC1-act (p=0.036), but *TSC1* alterations were not (p=0.63). In a pan-sarcoma population, high ssGSEA mTORC1-act scores were associated with lower median OS of 15.4 months (m) compared to intermediate (24.2 m) and low (36.8 m) mTORC1-act scores ($p<0.000001$). Similar findings were observed for LMS (16.2 v 30.6 v 45.9 m, $p<0.0001$) and LPS (11.2 v 30.1 v 46.8 m, $p<0.0001$), but not all subtypes. **Conclusions:** The high levels of mTORC1-act in PEComa and osteosarcoma are consistent with prior reports. Increased mTORC1-act among *TSC2*-mutant, but not *TSC1*-mutant, PEComa aligns with lower responses to mTORi observed in non-*TSC2*-mutant patients in the AMPECT trial. Together, these findings support the use of ssGSEA to identify histologic subtypes (UPS, IMT, epithelioid) and genetic factors (*TSC2* variants > others) associated with increased mTORC1 activity that may predict for better responses to mTORi, and they suggest a clinical trial to further pursue this pathway in sarcomas. These data provide additional valuable prognostic information for patients with a wide range of sarcoma subtypes. Research Sponsor: None.

11545 Poster Session

New soft tissue sarcoma (STS) transcriptomic clusters to unveil STS subsets with unique biological characteristics and refine the accuracy of overall survival (OS) prediction.

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Background: The currently used histopathological classification (HPC) is eminently morphological and error prone, fragmenting STS in 80 subtypes. Adding fragmentation to STS's rarity limits the deployment of pre-clinical and clinical research, hampering drug discovery and development. Finding new classification tools that better reflect STS's biology and that show predictive and prognostic value is an unmet need. **Methods:** FFPE samples of 25 dedifferentiated liposarcomas (DDLPS), 25 leiomyosarcomas (LMS), and 52 undifferentiated pleomorphic sarcomas (UPS) were analyzed along with clinical data from the patients. DNA and RNA were isolated. RNA sequencing was performed using the FoundationOne RNA assay. Normalized gene expression (GE) data (RUO) was analyzed using unsupervised machine learning and consensus clustering. 4 transcriptomic clusters (TC) were identified. A subsequent differential GE analysis between TC was done using limma. The Cox Proportional Hazards Model (CPHM) was used to evaluate the predictive ability of clinical variables, including HPC, and TC on OS, followed by an ANOVA test over CPHM results (AoC). The TCGA-SARC dataset was used for validation, classifying samples with our TC specific gene signatures via ssGSEA. Samples were classified to the TC with the lowest significant FDR adjusted p-value. This classification was integrated into a CPHM analysis of TCGA-SARC OS. **Results:** TC 1 (C1) (52.4% DDLPS, 19.0% LMS, 28.6% UPS) is characterized by overexpression (OE) of genes as CDK4 and under-expression (UE) of homologous recombination repair genes, such as BRCA. Over representation analysis identified UE of cell cycle and proliferation pathways. TC 2 (C2) (12.5% DDLPS, 29.2% LMS, 58.3% UPS) is portrayed by OE of MAGE genes, and OE of pathways linked with transcriptional regulation. TC 3 (C3) (5% DDLPS, 10% LMS, 85% UPS) is marked by OE of HLA genes (and immune related pathways) and UE of the β-catenin pathway. TC 4 (C4) (11.1% DDLPS, 22.2% LMS, 66.7% UPS) is distinguished by OE of cell components pathways. The CPHM revealed that C2, C3 and C4 are negative prognostic factors (C2 (HR 5.10; 95% CI 1.810-14.34; P= 0.002), C3 (HR 4.47; 95% CI 1.386-14.45; P= 0.01), C4 (HR 7.66; 95% CI 2.056-28.53; P= 0.002)).The CPHM and the AoC revealed that TC display the best ability to predict OS, being the only variable with a statistically significant correlation with OS (AoC ($P<0.01$)). Validation with TCGA-SARC showed an enrichment to C1 and C3. C3 enriched samples show a worse prognosis (HR 2.28; 95% CI 1.228-4.2; P= 0.009) and TC emerged, again, as the most significant variable for OS prediction (AoC ($P<0.01$)). **Conclusions:** RNA sequencing and a machine learning-based analysis identified 4 TC with distinct molecular characteristics (with potential specific predictive value) and superior accuracy for OS estimation when compared with HPC. Research Sponsor: Roche-Foundation Medicine.

11546 Poster Session

Immune infiltrate analysis to reveal distinct immune classes for leiomyosarcomas.

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Background: Leiomyosarcomas (LMS) are aggressive malignancies of smooth-muscle origin. Few targeted molecular options exist and immunotherapy (IO) agents against T cells have been disappointing. In this study, we examine the immune infiltrate of LMS tumors by immunohistochemistry (IHC) and gene expression. Our objective was to identify actionable targets for immunotherapy in patients with LMS. **Methods:** Tumor samples from a series of LMS patients were prospectively collected and banked for DNA and RNA sequencing as part of the MD Anderson Patient Mosaic. Associated clinical data for the patients were collected and maintained. IHC was performed on available separate tissue microarrays. Differential gene expression (DGE) analysis was done using the DESeq2 package for R and the Benjamini-Hochberg procedure used to control for false discovery rate. Immune cell fractions were estimated using the MCPcounter package. All gene expression analyses were repeated on The Cancer Genome Atlas (TCGA) dataset as an independent dataset. **Results:** A total of 104 TCGA samples and 72 samples from Mosaic from 53 patients with uterine or soft tissue LMS were included in the analysis. Tumors in the TCGA group were treatment naive. Of the samples in the Mosaic group, 61 (85%) had been previously treated with chemotherapy, 8 (11%) had been radiated, and 5 (7.5%) had been previously treated with immunotherapy. Thirty-one (43%) tumors were metastatic. Fifty-one (70%) were soft tissue LMS and 21 (30%) were uterine LMS. Four distinct immune classes were seen in both the TGCA and Mosaic: a predominantly B-cell group, a monocyte/macrophage group, a mixed infiltrate group and a group with a neutrophil signature. DGE performed between the subgroups revealed a unique gene expression pattern for tumors in the B cell and monocyte/macrophage subgroups. Interrogation of specific immune-associated genes revealed low levels of expression in the neutrophil group, suggesting this may be the most immunologically “cold” subset. Some of these results were reproduced by IHC using a TMA: the presence of a cluster of samples with B-cells and higher expression of immune checkpoints, a macrophage driven cluster, and an immunologically cold cluster. **Conclusions:** Analyses of LMS samples across two large datasets demonstrate the existence of 4 distinct immune classes of tumors that persist despite variation in clinical and treatment conditions: B cell, monocytic/macrophage, mixed-infiltrate and neutrophil rich. The B cell and monocytic groups have increased expression of immune markers which may be amenable to targeted therapies. Research Sponsor: None.

11547 Poster Session

A phase 2 trial of the CDK4 inhibitor dalpiciclib in well-differentiated or dedifferentiated liposarcoma.

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Background: The oncogene cyclin-dependent kinase 4 (CDK4) is amplified in > 90% of well-differentiated liposarcomas (WDLS) and dedifferentiated liposarcomas (DDLS). Previous studies have already demonstrated the clinical benefit of CDK4 inhibitors in the treatment of WDLS and DDLS. Dalpiciclib is a more potent and novel CDK4 inhibitor. We designed a multi-center phase 2 study to evaluate the safety and efficacy of dalpiciclib in patients with advanced WDLS/DDLS. **Methods:** Eligible patients were adults aged 18 years and older, with a confirmed diagnosis of advanced WDLS/DDLS, measurable lesions according to RECIST 1.1, any (or no) priory therapy, and a history of progression by RECIST 1.1 in the 6 months prior to enrollment. All patients were required to have CDK4amplification by fluorescence in situ hybridization and retinoblastoma (RB) protein expression by immunohistochemistry. All patients were treated with dalpiciclib 150 mg orally once per day for 21 consecutive days within a 28-day treatment cycle. The primary endpoint was progression free survival (PFS) at 12 weeks. Secondary end points included objective response rate and adverse events. **Results:** From August 2022 to October 2023, a total of 32 patients were enrolled, and 30 were evaluable for the primary end point. Median (range) age was 59 (40-76) years; 22 patients (69%) were male. At 12 weeks, PFS was 61.3% (95% CI, 44-78.5%). The median PFS was 17.4 weeks (95% CI, 10.65-24.15 weeks). Only one patient had a partial response to the treatment. Grade 3 to 4 events included neutropenia (37.5%), anemia (6.25%), thrombocytopenia (6.25%), and nausea (3.13%). **Conclusions:** Treatment with the CDK4 inhibitor dalpiciclib was associated with a favorable PFS rate in patients with advanced CDK4-amplified and RB-expressing WDLS/DDLS. Clinical trial information: ChiCTR2200062868. Research Sponsor: None.

11548 Poster Session

Phase IIA study of high-affinity TCR-T (TAEST16001) targeting NY-ESO-1 in soft tissue sarcoma.

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Background: TAEST16001 cells are genetically engineered autologous T cells expressing high-affinity NY-ESO-1-specific T-cell receptor (TCR) targeting NY-ESO-1 (expressed in a wide range of tumors) positive soft tissue sarcoma (STS) in the context of HLA-A*02:01. A phase I study of in patients with advanced STS (NCT04318964) demonstrated safety and preliminary indication of efficacy at ASCO 2022. Here, we will present our encouraging phase IIa results. **Methods:** This is an open-labeled, single arm study to evaluate efficacy and safety of TAEST16001 cells in patients with advanced STS (NCT05549921). Enrolled patients underwent apheresis, their isolated T cells expanded *in vitro* after transduction with a lentiviral vector expressing high affinity NY-ESO-1 TCR. Patients received 3-day lymphodepleting chemotherapy (cyclophosphamide 15 mg/kg/day and fludarabine 20 mg/m^2/day). TAEST16001 cells were administered at $1.2 \times 10^{10} \pm$ 30% cells (determined through our phase I data) and they also received 14-day IL-2 s.c. injection. Target efficacy (*per* RECIST 1.1) was set at overall response rate (ORR) =25% for the first stage cohort of 12 patients. **Results:** As of January 2024, 8 patients were enrolled (M:F 4: 4; mean age: 40 yrs.; median prior regimens: 3 (range:2-5)). TAEST16001 cells demonstrated a manageable safety profile consistent with previous phase I study. The common (n>1) reported grade (G) 3 adverse events were lymphocytopenia (n=8), decreased WBC count (n=7), neutropenia (n=6), elevated γ-GT (n=3), hypokalemia (n=2). Six patients had cytokine release syndrome (CRS) (G3: 1; G2: 1; G1: 4), and 2 patients also experienced G1 ICANS, all resolved completely after symptomatic treatment. Importantly, after at least two tumor assessments, 4 had confirmed partial response, 3 had stable disease, and 1 had progressive disease. The ORR at cut-off date was 50%. The median time to initial response was 1.1 months (1.1 to 2.2) and median duration of response was 5.0 months (1.5 to 8.8). Most patients are still being follow-up. When pooling the data for the same dose in phase I part, ORR at dose of 1.2×10^{10} was 54.5% (6/11). **Conclusions:** TAEST16001 demonstrated an acceptable safety profile. The encouraging efficacy data (ORR=50%) exceeded our pre-specified target efficacy (ORR=25%). The review committee has recommended TAEST16001 to proceed early to the next stage of clinical development. Clinical trial information: NCT05549921. Research Sponsor: None.

11549 Poster Session

Efficacy and safety of SHR-2554 in advanced epithelioid sarcoma: A phase 2 trial.

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Background: Epithelioid sarcoma (ES) is a rare and aggressive subtype of soft-tissue sarcoma. The loss of SMARCB1 (INI1) expression which leads to oncogenic dependence on the transcriptional repressor EZH2 has been observed in over 90% of ES. Patients (pts) with metastatic ES have a poor prognosis. We investigated the efficacy and safety of SHR-2554, an oral selective EZH2 inhibitor, in pts with refractory ES. **Methods:** To be eligible for inclusion, pts had to fulfill the following criteria: 8 years or older; histologically confirmed advanced or metastatic ES with loss of INI1 or upregulated mRNA level of EZH2; progressive disease after at least one line of doxorubicin-containing chemotherapy; the presence of measurable disease according to RECIST 1.1; an ECOG performance status of 0-1. Pts received SHR2554 (350 mg, bid, po) until disease progression or unacceptable toxicity. The primary endpoint was progression-free rate at 12 weeks. A Simon two-stage design was applied. If there were 3 pts remaining progression-free at 12 weeks within the first 9 pts, the cohort would expand to 17 pts and the outcome would be positive if more than 7 pts remained progression-free at 12 weeks. **Results:** Between Jul 2021 and Dec 2023, a total of 17 pts were enrolled and received at least 1 dose of SHR-2554. The median age was 32 years (range 8-57) and 41.2% were males. 9 (52.9%) pts had received immunotherapy targeting PD-1/L1 and 6 (35.3%) pts had received anti-angiogenesis therapy before enrollment. The median line of previous treatment was 2 (range 1-4). Loss of INI1 was confirmed in 14 (82.4%) pts. Tumor response was evaluated in 14 pts at data cutoff. 9 (64.3%) of 14 pts remained progression-free at 12 weeks. The primary endpoint was met. Based on investigator assessment, 3 (21.4%) of 14 pts achieved partial response and 8 (57.1%) pts had stable disease as best response. Adverse events (AEs) were generally mild. The most common treatment-related hematological AEs were anaemia, platelet count decreased and hyperuricaemia. **Conclusions:** SHR-2554 showed promising efficacy and an acceptable safety profile in pts with refractory ES, warranting further investigation. Clinical trial information: ChiCTR2100046099. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

11550 Poster Session

A potential novel therapeutic target for invasive soft tissue sarcoma detected through tumor immune microenvironment and genetic profile analyses.

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Background: Improvements in surgical techniques and the introduction of perioperative chemotherapy have led to the improved 5-year survival rate of 91% for bone and tissue sarcoma in Japan (JCOG1306 trial). However, for invasive soft tissue sarcomas, the local control rate remains approximately 80% with a high recurrence rate. Undifferentiated pleomorphic sarcoma (UPS) and myxofibrosarcoma (MFS) frequently exhibit strong local invasiveness, yet the mechanisms underlying their invasiveness remain unclear. Thus, in this study, we aimed to explore the tumor microenvironment and genetic profiles associated with the invasiveness of UPS and MFS by using bulk RNA-sequencing data. **Methods:** We focused on 47 cases with UPS or MFS, whose RNA-sequencing data were obtained from surgical specimens at the Cancer Institute Hospital of JFCR between April 2017 and April 2023. The entire cohort was divided into two groups based on preoperative MRIs. Tumors showing a tail-like sign or irregular margins were categorized as invasive (Group I: 32 cases, average age 71±13 years, UPS 22 cases, MFS 10 cases), while tumors with clearly defined margins were categorized as non-invasive (Group NI: 15 cases, average age 68±13 years, UPS 10 cases, MFS 5 cases). We calculated immune cell fractions using CIBERSORTx and analyzed the differentially expressed genes (DEGs) and altered pathways using iDEP estimated from RNA-sequencing data. The results were analyzed for correlation with clinical outcomes. **Results:** The 5-year overall survival rate was significantly lower in Group I (74%) than in Group NI (100%, p=0.04), while the 5-year recurrence-free survival rate did not differ significantly between the groups (p=0.4). Group I showed significantly lower naive B cell count (p=0.04), and cases with higher naive B cell count had a significantly higher 5-year overall survival rate than those with lower count (93% vs. 69%, p=0.04). A total of 1260 DEGs were identified between Group I and NI, including 241 immune-related genes, and 11 genes were associated with overall survival. Multivariate analysis of these 11 immune-related genes and overall survival revealed the significant association of one gene, "Gene X" (p=0.01). In Group I, pathways related to fat metabolism were downregulated, while those related to sugar metabolism and rheumatoid arthritis were upregulated. **Conclusions:** This study revealed that soft tissue sarcoma invasiveness is correlated with overall survival. Specific tumor-infiltrating immune cells and immune-related genes may be regulated by the associated metabolic pathways. The pathways including "Gene X", which reported with its antibodies, may contribute to the regulation of invasiveness of invasive soft tissue sarcoma and the improvement in survival rate. Thus, "Gene X" may be considered a potential novel therapeutic target for invasive soft tissue sarcoma. Research Sponsor: None.

11551 Poster Session

Results of a randomized phase II trial of 2nd-line treatment for advanced soft tissue sarcoma comparing trabectedin, eribulin and pazopanib: Japan Clinical Oncology Group study JCOG1802 (2ND-STEP).

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Background: Trabectedin, eribulin, pazopanib, and gemcitabine plus docetaxel (GD) are the candidates of second-line chemotherapy for advanced soft tissue sarcomas (STS), although there is no clear evidence showing which is better among those agents. This clinical trial aims to determine the most promising regimen among trabectedin, eribulin, and pazopanib as the test arm regimen in the future phase III trial of the second-line treatment for patients with advanced STS. **Methods:** This study, JCOG1802, is a multicenter randomized phase II selection design trial comparing trabectedin (1.2 mg/m^2 IV, every 3 weeks), eribulin (1.4 mg/m^2 IV, days 1 and 8, every 3 weeks) and pazopanib (800 mg PO, everyday) for patients with unresectable or metastatic STS refractory to doxorubicin-based first-line chemotherapy. Eligibility criteria include 16 years old or older, ECOG performance status of 0–2, unresectable and/or metastatic STS, an exacerbation within 6 months prior to registration, histological diagnosis of STS other than Ewing sarcoma, well-differentiated liposarcoma and myxoid liposarcoma, a history of chemotherapy of doxorubicin-based regimen for STS, and sufficient organ function. Primary endpoint is progression-free survival (PFS), and secondary endpoints include overall survival (OS), disease-control rate (DCR), response rate (RR), and adverse events. The planned total sample size was set at 120 patients to select the most promising regimen with a probability of at least 80%, assuming a median PFS of 3 months in the worst regimen and 4 months in the best regimen. The regimen demonstrating the most favorable point estimate of hazard ratio for PFS is chosen for the subsequent phase III trial. **Results:** From December 2019 to March 2023, 120 patients with advanced STS were enrolled (31 with leiomyosarcomas, 26 with liposarcomas, 18 with translocation-related sarcomas, and 45 with others) and randomized. Median PFS for trabectedin was 2.9 months (95% CI 1.3-5.3), for eribulin was 2.2 months (1.5-3.8), and for pazopanib was 3.7 months (2.6-5.2), respectively. The hazard ratios for eribulin and pazopanib compared to trabectedin were 1.22 (0.77-1.94) and 0.99 (0.63-1.56), respectively. Median OS for trabectedin was 14.8 months (10.8-29.1), for eribulin was 13.3 months (7.6-20.1), and for pazopanib was 15.7 months (9.8-not estimable). DCR for trabectedin was 50.0% (32.4-67.6), for eribulin was 34.3% (19.1-52.2), and for pazopanib was 64.9% (47.5-79.8). **Conclusions:** Pazopanib showed the best PFS and OS as the second-line treatment for patients with advanced STS among trabectedin, eribulin, and pazopanib. A phase III trial comparing GD with pazopanib is planned as the next step. Clinical trial information: jRCTs031190152. Research Sponsor: Japan Agency for Medical Research and Development (AMED); 23ck0106764.

11552 Poster Session

Phase IB/II trial of durvalumab plus doxorubicin combination in patients with advanced soft-tissue sarcoma.

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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 trial (NCT03798106), we enrolled patients with metastatic and/or recurrent STS had not received anthracycline chemotherapy and PD-L1/PD-1 inhibitor. Phase IB assessed the safety and tolerability of doxorubicin [level 1 (75mg/m^2) and level -1 (60 mg/m^2)] in combination with durvalumab 1500 mg once every 3 weeks until documented disease progression or unacceptable toxicity. Phase II assessed the efficacy, with the primary endpoint to detect a difference in objective response between 5% and 20%. **Results:** No DLTs were observed during the phase IB (n=3), therefore recommended phase II dose was defined at doses of 75/m^2 doxorubicin and proceed the phase II part. Of 41 evaluable patients, 1 (2.4%) achieved complete response, 12 (29.3%) achieved confirmed partial response, yielding an objective response rate of 31.7%. 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). Treatment-related adverse events of grade 3 or 4 occurred in neutropenia (n = 23, 53.4%), thrombocytopenia (n=6, 13.9%), and anemia (n=5, 11.6%). The prespecified genomic analysis with targeted and transcriptomic sequencing will be available at the meeting. **Conclusions:** Durvalumab combined with doxorubicin demonstrated promising efficacy in an unselected STS cohort, with a manageable toxicity profile. Clinical trial information: NCT03798106. Research Sponsor: None.

11553 Poster Session

Redefining radiologic responses (RR) in solid tumors: Shall we brace ourselves for a post-RECIST era? Results from a randomized clinical trial (RCT) on neoadjuvant chemotherapy in high-risk soft-tissue sarcomas (HR-STS) of the trunk or extremities.

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Background: ISG-STS 1001, a RCT comparing anthracycline + ifosfamide (AI) vs. histology-tailored (HT) neoadjuvant chemotherapy (N) in primary localized HR-STS (G3; d >5 cm; deeply seated) showed superiority of AI, especially in the higher risk group. We report the results of the planned secondary analysis of RR. **Methods:** Patients (pts) with undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma (LMS), malignant peripheral nerve sheath tumor (MPNST), synovial sarcoma (SS) or myxoid liposarcoma (MLPS) were randomized, whereas pts with myxofibrosarcoma (MFS), pleomorphic liposarcoma (PLPS), pleomorphic rhabdomyosarcoma (PRMS) or unclassified sarcoma (US) were included in the observational arm (O). Pts with UPS, LMS or MLPS needing concurrent preoperative radiotherapy (RT) were included in O. Primary endpoint was Disease Free Survival (DFS). Planned secondary endpoints included Overall Survival (OS) and centrally reviewed RR per RECIST 1.1. Associations between DFS/OS and RR (per RECIST and as percent dimensional variation (D), dichotomized and continuous), DFS/OS and histology, and RR and histology were evaluated via Cox regression models. **Results:** 435 pts were included: 287 were randomized and 148 included in O. This analysis comprised all 236 pts with measurable disease and centrally reviewed RR. RECIST best responses were: 28 (11.9%) partial response (PR), 195 (82.6%) stable disease (SD), 13 (5.5%) progressive disease (PD). RR per RECIST significantly correlated with both DFS (PD vs PR: HR 8.2, 95% CI 3-22.6; SD vs PR: HR 3.0, 95% CI 1.3-6.8) and OS (PD vs PR: HR 12.6, 95% CI 3.4-46.8; SD vs PR: HR 4.2, 95% CI 1.3-13.5). A concordant yet not statistically significant trend for DFS was observed in pts who received N (AI or HT) without RT (157 pts; PD + SD vs PR: HR 2.2, 95% CI 0.8-6.1) and those who received AI without RT (93 pts; PD + SD vs PR: HR 2.4, 95% CI 0.8-7.9). To rule out confounding factors, we proved no significant correlation existed between histology and RR per RECIST. We computed the median value of D (-1.6%) and demonstrated that pts with D > -1.6% had worse clinical outcomes than those with D < -1.6% (DFS: HR 1.7, 95% CI 1.2-2.5; OS: HR 1.9, 95% CI 1.2-2.9), and that D in continuous scale significantly correlated with both DFS (HR 1.5, 95% CI 1.3-1.9) and OS (HR 1.8, 95% CI 1.4-2.3). This suggests any D proportionally impacted DFS/OS **Conclusions:** These results confirm the independent prognostic value of RR both per RECIST and D in selected HR-STS treated with N, and hint that arbitrary thresholds may be divested, as any change in size allows to infer the proportional efficacy of treatment. The greater the dimensional reduction, the stronger the positive influence on clinical outcome; the greater the increase in size, the stronger the corresponding detrimental effect Clinical trial information: NCT01710176. Research Sponsor: None.

11554 Poster Session

An open label, phase 1b/2 trial of LVGN6051 (4-1BB agonistic antibody) combined with anlotinib for refractory soft tissue sarcoma (STS).

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Background: Refractory soft tissue sarcoma has limited treatment options. LVGN6051 is a conditional 4-1BB agonistic mAb with Fcγ-receptor IIB selective binding in the tumor microenvironment for optimal activity. Anlotinib has been approved for STS in China. Combining immune agonistic and anti-angiogenetic agents for refractory STS warrants a clinical study. **Methods:** We conducted phase 1b dose finding with a 3+3 design and phase 2 efficacy exploration by tumor response with Simon's two-stage design. Eligible pts with anthracycline refractory locally advanced or metastatic STS received escalating doses of LVGN6051 (1, 2, 3, 4 mg/kg) I.V. q3w plus anlotinib 10 mg or 12 mg per body surface area P.O. day 1-14 q3w in phase 1b, and RP2D as LVGN6051 3 mg/kg plus a standard dose of anlotinib in Phase 2. **Results:** As of Jan 22, 2024, a total of 39 pts, 18 in phase 1b and 21 in phase 2, were enrolled and received study treatment with LVGN6051 and anlotinib. The median age was 40 years (range 21-66), and the median number of prior systemic therapies was 2; 31 pts (79%) had ECOG PS 1, and 20 pts (51%) had received prior immune checkpoint inhibitors (ICI). In phase 1b, 1 DLT was observed in the LVGN6051 3 mg/kg plus anlotinib cohort and 2 DLTs in the LVGN6051 4 mg/kg plus anlotinib cohort. All those 3 DLTs were Gr 4 thrombocytopenia. LVGN6051 3 mg/kg IV Q3W plus a standard dose of anlotinib was selected as RP2D. Phase 1b/2 pts received a median of 3 cycles and a mean of 6.0 cycles (range 1.0 – 20.0) of study treatment. 38 out of 39 pts (97.44%) experienced any grade treatment-related adverse events (TRAEs). 24 pts (61.54%) showed $\geq$ grade 3 TRAEs, of which $>$10% TRAEs included thrombocytopenia (43.59%), AST increased (12.82%), WBC count decreased (10.26%), and neutrophil count decreased (10.26%). Most TRAEs occurred during the first or second cycle of study treatment and were transient, which recovered within 1-2 weeks with clinical symptomatic treatment. Per RECIST 1.1, in 29 efficacy-evaluable pts, the disease control rate was 86.21% with 2 PR and 23 SD. The two PR pts: 1 leiomyosarcoma got a tumor shrinkage of 40.3% at week 21 and now a total of 12 cycles of study treatment, and 1 undifferentiated pleomorphic sarcoma got 36.01% at week 6 and now 3 cycles. Among the SD pts, 4 reached near-PR: 1 synovial sarcoma got 29.03% at week 12 and now 14 cycles, 1 alveolar soft part sarcoma (ASPS) got 28.57% at week 6 and now 14 cycles, 1 epithelioid sarcoma got 28.72% at week 30 and now 10 cycles, and another ASPS got 28.45% at week 57 and now 19 cycles. All above PR and near-PR pts are still under study treatment. **Conclusions:** LVGN6051 plus anlotinib was well tolerated, and the RP2D is LVGN6051 3 mg/kg plus a standard dose of anlotinib. The combination showed preliminary and encouraging efficacy for refractory STS. As the study is ongoing, additional data will further validate the safety and efficacy of such combination therapy for refractory STS. Clinical trial information: NCT05301764. Research Sponsor: None.

11555 Poster Session

Phase 2a results of SQ3370, a doxorubicin-based click chemistry therapeutic in patients with advanced STS: Planned interim analysis.

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Background: Shasqi is a clinical stage biotech that uses click chemistry, a Nobel Prize winning technology, to selectively activate cancer treatments at the tumor. The Click Activated Protodrugs Against Cancer (CAPAC) platform comprises of 1) tumor targeting agents, which carry an activator, and 2) attenuated cancer drugs, which are selectively activated at the tumor by the targeting agent through click chemistry, maximizing therapeutic index and minimizing toxicities. We have demonstrated clinical proof of concept with SQ3370, which uses an intratumorally injected SQL70 biopolymer (bp) with a doxorubicin (Dox) protodrug (SQP33) injected systemically. As previously reported RP2D of SQP33=12x Dox. (NCT04106492). **Methods:** Dox naïve patients (pts) received 10/20 mL bp and protodrug IV QD x 3 or 5. Key eligibility: locally advanced or metastatic soft tissue sarcomas (STS). The objective was to explore bp dose and schedule of the RDP2 (same dose per cycle) in advanced or metastatic STS. **Results:** Fourteen patients with predominantly metastatic (11/14) STS, all unresectable, were enrolled at the 1st interim analysis. Median age 58 years (32-89), ECOG=1 (11/14). Therapy was well tolerated. The most common TEAE was nausea and fatigue (all grade $\leq$ 2), with 1 subject in each group having a manageable grade $\leq$ 3 TEAE-related discontinuations. The majority of subjects did not suffer clinical myelosuppression grade $\leq$ 1 neutropenia (10/14), anemia (13/14), or thrombocytopenia (13/14), with DCR 71% (CI 95% 44-92%) and ORR 14.3% (CI 95%1.7-40%). Detailed PK, immune assessment and safety findings will be presented. **Conclusions:** SQ3370 is the first clinical click chemistry-based cancer therapy, and this is the 1st clinical trial to explore doses greater than 3x Dox in STS patients. The results show that the bp activates protodrug, which is not a vesicant, and releases Dox in patients. Click chemistry favorably alters PK and safety of the Dox payload. At 12x Dox, using the commonly administered 3-week schedule, Dox was very well tolerated. Click-chemistry maintains expected clinical activity, and preliminary data suggest enhanced safety (reduced myelosuppression) as well as unlocking immunological effects (intratumoral and systemic), without the myelosuppressive effects typically seen with Dox. Clinical trial information: NCT04106492. Research Sponsor: Shasqi.

Group (N)	STS Population	BP Dose	Days SQP33
1 (2)	Treatment naïve extremity unresectable/met.	20 mL	5
2a (6)	Unresectable/met.	10 mL	3
2b (6)	Unresectable/met.	10 mL	5

Efficacy of nirogacestat in participants with poor prognostic factors for desmoid tumors: Analyses from the randomized phase 3 DeFi study.

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Background: Desmoid tumors (DT) are rare, locally aggressive, soft-tissue tumors with a highly unpredictable natural course and substantial patient burden, including pain and functional limitations. Prognosis of DT is potentially dependent on multiple factors, including tumor location, size, patient's age, mutational status, and presence of pain. Nirogacestat (niro), a targeted gamma secretase inhibitor, is the only treatment approved in the US for adults with progressing DT. In the phase 3 DeFi study, niro demonstrated significant and clinically meaningful improvement vs placebo (pbo) in the primary and key secondary endpoints of progression-free survival (PFS: HR, 0.29 [95% CI: 0.15-0.55]; $P<.001$), objective response rate (ORR: 41% vs 8%; $P<.001$), and patient-reported outcomes (pain, DT-specific symptom burden, physical and role functioning, and overall quality of life; $P\leq0.01$, all). The objective of this analysis was to determine the effect of niro in patient subgroups that have been associated with poor prognosis (larger tumor size, younger age, *CTNNB1* mutation types, and pain). **Methods:** DeFi (NCT03785964) was a global, multicenter, double-blind study to determine the efficacy, safety, and tolerability of niro in adults with progressing DT. Patients were randomized 1:1 to niro 150 mg (n=70) or pbo (n=72), taken twice-daily in 28-day cycles. Post hoc analyses of PFS and ORR were conducted in individuals stratified by patient- and tumor-related prognostic factors. **Results:** PFS and ORR improvement favored niro vs pbo regardless of the patient subgroup, including: baseline tumor size (≤10 cm, >10 cm); age (≤30 y, >30 y); *CTNNB1* mutation type (S45F, T41A); and baseline pain (uncontrolled, controlled) (Table). Across the subgroups analyzed, PFS hazard ratio ranged from 0.18 to 0.39, with values <1 favoring niro over pbo. ORR risk difference (niro – pbo) ranged from 18.1% to 56.0%, with values >0 favoring niro. **Conclusions:** Niro demonstrated consistent improvement in PFS and ORR vs pbo in patients with characteristics implicated as poor prognostic factors for DT—including larger tumor size, younger age, *CTNNB1* mutation types, and pain. These results indicate that niro can provide substantial benefit across the subgroups analyzed. Clinical trial information: NCT03785964. Research Sponsor: SpringWorks Therapeutics, Inc.

Subgroups	PFS Hazard Ratio (95% CI) (<1 favors niro)	ORR Risk Difference, % (niro – pbo; >0 favors niro)
Tumor size		
≤10 cm	0.27 (0.11, 0.70)	45.8
>10 cm	0.32 (0.13, 0.80)	18.1
Age		
≤30 y	0.21 (0.08, 0.60)	36.3
>30 y	0.34 (0.15, 0.81)	31.4
***CTNNB1* mutation**[a]		
S45F	0.18 (0.02, 1.46)	56.0
T41A	0.39 (0.14, 1.11)	24.2
Baseline pain[b]		
Controlled: ≤4	0.25 (0.10, 0.61)	27.2
Uncontrolled: >4	0.37 (0.14, 0.95)	41.7

[a]Small patient numbers limited analysis of wild-type.
[b]Brief Pain Inventory Worst Pain score. Literature recognizes the presence of any pain as a poor prognostic factor; this analysis categorized pain as controlled and uncontrolled.

11557 Poster Session

Safety and toxicity evaluation of the combination of selinexor with atezolizumab in patients with soft tissue sarcomas.

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Background: The U.S. Food and Drug Administration (FDA) recently approved the anti-PD-L1 antibody atezolizumab for alveolar soft part sarcoma (ASPS). Selinexor, a selective XPO1 inhibitor, demonstrated cytotoxic activity in ASPS-KY and ASPS-1 cell lines of ASPS and other sarcoma cell lines; it has been approved as a part of regimens to treat multiple myeloma and diffuse large B-cell lymphoma. Preliminary clinical data demonstrate acceptable safety profiles in patients with melanoma who received selinexor in combination with an anti-PD-1 antibody. **Methods:** We designed a randomized phase 2 study to evaluate atezolizumab with or without selinexor in adult patients with ASPS that included a safety run-in (SR) open to patients with soft tissue sarcoma (NCT05333458). Prior immune checkpoint inhibitor therapy was not allowed. During the SR, patients received selinexor (60 mg PO) on days 1, 8, and 15 of the 28-day cycle and atezolizumab (1200 mg flat dose IV) on day 8 at the Developmental Therapeutics Clinic. Protocol-defined treatment-related adverse events (TRAEs) occurring during cycle 1 would either expand accrual to the SR or close the study. Safety data were evaluated by the principal investigator and NCI CTEP (National Cancer Institute Cancer Therapy Evaluation Program). **Results:** Six patients were enrolled in the SR and were evaluated weekly during the first cycle of study treatment. All patients were female with a median age of 47 years (range: 22-71 years). Diagnoses included sclerosing epithelioid fibrosarcoma (n=2), dedifferentiated liposarcoma (n=1), metastatic leiomyosarcoma (n=1), metastatic angiosarcoma (n=1), and ASPS (n=1). No patients were removed from the SR due to AEs. Two patients experienced grade 3 TRAEs, including one instance each of neutropenia and lymphopenia (Table). Beyond cycle 1, there was 1 occurrence of grade 3 lymphopenia. No grade 4 or 5 AEs have occurred during the SR. Fatigue and nausea were the most prevalent TRAEs, but only one patient experienced grade 2 nausea; all other occurrences of nausea and fatigue were at grade 1. **Conclusions:** The safety run-in completed without any occurrences of protocol-defined treatment-related toxicity during cycle 1. The treatment was well tolerated. Based on these data, the randomized part of this study began accruing patients with ASPS across the ETCTN (Experimental Therapeutics Clinical Trials Network). Clinical trial information: NCT05333458. Research Sponsor: None.

Highest grade TRAEs occurring in ≥2 participants during cycle 1.

Adverse Event	Participants (%)	Grade 1	Grade 2	Grade 3
Fatigue	5 (83)	5		
Nausea*	5 (83)	4	1	
Hyponatremia	3 (50)	2	1	
Lymphopenia	3 (50)	2		1
Leukopenia*	3 (50)	1	2	
Vomiting*	3 (50)	1	2	
Anemia	2 (33)	1	1	
Neutropenia*	2 (33)		1	1
Thrombocytopenia	2 (33)	2		

*These TRAEs were present at more than 1 clinic visit for at least 1 participant during cycle 1 and the highest grade is listed for participants with multiple occurrences.

11558 Poster Session

Efficacy and safety of nirogacestat in patients with desmoid tumor and *adenomatous polyposis coli (APC)* mutation: Phase 3 DeFi analyses.

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Background: Nirogacestat (niro) is a targeted and selective gamma secretase inhibitor approved in the US for adults with progressing desmoid tumors (DT). In the phase 3 DeFi study, niro demonstrated significant improvement vs placebo (pbo) in progression-free survival (PFS: HR, 0.29 [95% CI: 0.15-0.55]; $P<.001$), objective response rate (ORR: 41% vs 8%; $P<.001$); and patient-reported outcomes (PROs) of pain, DT-specific symptom burden, physical and role functioning, and overall quality of life ($P\leq.01$, all). DT are driven by Wnt/β-catenin signaling pathway alterations and about 10-20% of DT are associated with mutations in the *APC* tumor suppressor gene, which may confer more aggressive DT behavior. Because patients with *APC* mutations may do worse, regardless of specific therapy, a post hoc analysis was conducted to assess effects of niro in patients with progressing DT and *APC* mutations. **Methods:** DeFi was a global, double-blind study that evaluated the efficacy, safety, and tolerability of niro in adults with progressing DT. Patients were randomized to oral niro (150 mg) or pbo twice-daily in continuous 28-day cycles. Descriptive post hoc analyses were conducted to assess effects of niro in patients with somatic and/or germline *APC* mutations. **Results:** Among 29 patients in DeFi with *APC* mutations (niro=13; pbo=16), 19 (66%) were female, 16 (55%) were aged ≤30 years, and 22 (76%) were refractory to prior treatment (with a median of 3 prior lines of treatment). In patients with *APC* mutation, PFS was improved with niro vs pbo (HR, 0.21 [95% CI: 0.05-1.00], $P=.016$). Confirmed ORR was 38% (5/13) for niro vs 13% (2/16) for pbo. Niro-treated patients also had greater reduction in median best percent change from baseline compared with pbo-treated patients in target tumor size (-29.5 vs +2.2), volumetric MRI (-71.0 vs +5.4), and T2 hyperintensity (-74.1 vs -21.0). Across all PROs assessed — Brief Pain Inventory, GODDESS DT Symptom Scale and DT Impact Scale, and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 — patients treated with niro had numerically greater improvement from baseline at cycle 10 than pbo. Analyses were limited due to the small sample size. Adverse events in >50% of niro-treated patients with *APC* mutation were diarrhea, nausea, rash maculopapular, and fatigue; ovarian toxicity occurred in 9 of 10 of females of reproductive potential (6 resolved, 2 lost to follow-up, 1 ongoing and receiving niro). **Conclusions:** Improvement in PFS, ORR, tumor imaging characteristics and PROs was observed with niro compared to pbo in patients with DT harboring *APC* mutations. Efficacy and safety of niro in patients with *APC* mutations were generally consistent with findings for the overall DeFi population, suggesting that niro can provide clinically meaningful benefit to patients with progressing DT and *APC*mutations. Clinical trial information: NCT03785964. Research Sponsor: SpringWorks Therapeutics, Inc.

11559 Poster Session

Efficacy and safety of IBI110 (anti-LAG-3 antibody) plus sintilimab (anti-PD-1 antibody) in patients with advanced alveolar soft part sarcoma: Results from a phase II study.

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Background: Lymphocyte-activation gene 3 (LAG-3) has emerged as a novel target for immunotherapy (IO). Co-inhibition of LAG-3 and PD-1 may enhance immune checkpoint inhibition with synergistic effects. Herein, we report a phase II study evaluating the safety and efficacy of an anti-LAG-3 antibody (IBI110) plus sintilimab in patients (pts) with advanced alveolar soft part sarcoma (ASPS). **Methods:** Eligible pts with metastatic or unresectable ASPS were enrolled in two cohorts: cohort A (IO-naïve, defined as no history of previous immune checkpoint inhibitors, including but not limited to anti-PD-1/PD-L1/CTLA-4 antibodies) and cohort B (IO-failed, defined as imaging-confirmed disease progression after treatment with anti-PD-1/PD-L1 antibodies). All pts received IBI110 200 mg plus sintilimab 200 mg intravenously once every three weeks (Q3W). The primary endpoints were objective response rate (ORR) and progression-free survival (PFS), assessed by the investigator per RECIST v1.1, and safety. Secondary endpoints included overall survival (OS) and 6-month PFS rate. **Results:** As of January 20, 2024, the study enrolled 28 pts (males: 57.1%, median age: 30.5 years, ECOG PS 0: 100%; TNM stage IV: 100%; lung metastasis: 100%), including 20 pts in cohort A and 8 pts in cohort B. The median treatment duration was 11 cycles. There were 15 pts in cohort A and 4 pts in cohort B remaining on treatment as of the cutoff date. Response was evaluable in 27 pts. The best responses were 3 complete responses (CR), 8 partial responses (PR), and 9 stable diseases (SD) in cohort A; 2 PR and 5 SD in cohort B. ORR was 55.0% in cohort A and 28.6% in cohort B. The 6-month PFS rate was 94.7% in cohorts A and 66.7% in cohort B. At a median follow-up of 8.0 months, median PFS was not reached in cohort A and was 14.7 months in cohort B. Median OS was not reached in both cohorts. Treatment-related adverse events (TRAEs) occurred in 27 (96.4%) pts, including grade ≥3 TRAEs in 9 (32.1%) pts. The most frequent TRAEs were hyperuricemia (57.1%), increased blood lactate dehydrogenase (42.9%), and hypertriglyceridemia (42.9%), all of which were grade 1-2. Immune-related adverse events (irAEs) occurred in 27 (96.4%) pts, including grade ≥3 irAEs in 9 (32.1%) pts. Serious TRAE occurred in 2 (7.1%) pts with type 1 diabetes mellitus. TRAE leading to treatment interruption occurred in 1 (3.6%) pt due to type 1 diabetes mellitus. No TRAE led to treatment discontinuation or death. **Conclusions:** Co-inhibition of LAG-3 and PD-1 showed encouraging efficacy in pts with advanced ASPS. Compared to anti-PD-1 monotherapy, the combination treatment improved ORR in IO-naïve pts and restored IO effectiveness in previously IO-failed pts. The safety profiles were acceptable and manageable in all pts. Clinical trial information: MR-11-22-004975. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

Efficacy and safety of lurbinectedin (LUR) with irinotecan (IRI) in a phase 2 expansion cohort of patients (Pts) with synovial sarcoma (SS).

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Background: LUR has shown activity in several solid malignancies. Preclinical studies found synergism for LUR combined with IRI (Galmarini C. Cancer Res 2013; 73: Abst 5499). The phase 1b/2 study PM1183-A-014-15 (NCT02611024) evaluated the LUR/IRI combination in pretreated pts with advanced solid tumors. The recommended dose was defined at LUR 2.0 mg/m^2 on Day (D) 1 + IRI 75 mg/m^2 on D1, D8 q3wk with primary G-CSF prophylaxis. After observing 3 partial responses in SS pts during the phase 1b part, a phase 2 expansion cohort was implemented to explore this activity further. **Methods:** This cohort included pts with SS progressing after up to 2 prior cytotoxic-containing lines for advanced disease. The primary endpoint was overall response rate (ORR) per independent review committee (IRC)/investigator. **Results:** Thirty pts were enrolled and treated. Baseline characteristics were median age 41 y (range, 19-73), 57% males, 53% ECOG PS=1. Primary tumor location was mostly in the extremities (53%). Most common tumor metastatic sites at study entry were lung (83%), pleura (37%) and lymph nodes (23%). 60% had at least one lesion >50mm. The median number of prior lines was 2 (range, 1-5), and the median number of prior chemotherapy lines for advanced disease was 1 (range, 0-3). The median time from diagnosis was 32 mo (range, 2-160 mo). The best response to first-line therapy was stable disease in 50% of pts and progressive disease in 8%. Efficacy results are summarized (Table). Most common G3/4 events/abnormalities were neutropenia (60%), anemia (27%), thrombocytopenia (17%), diarrhea (10%), fatigue (10%) and febrile neutropenia (10%). 20% had treatment-related SAEs. No treatment-related discontinuations or deaths occurred. No evidence of drug-drug interaction was observed in the PK analysis. **Conclusions:** The LUR/IRI combination showed activity in pretreated SS with manageable toxicity. These results reinforce the rationale for assessing the activity of LUR combined with IRI in SS and other tumor types. Clinical trial information: NCT02611024. Research Sponsor: None.

Characteristics, efficacy and safety.

	Investigator (n=30)	IRC (n=26) [a]
Median no. of cycles (range)	5.5 (1-22)	
ORR, % (95% CI)	13.3% (3.8-30.7%)	19.2% (6.6-39.4%)
Median DoR, mo (95% CI)	5.7 (4.3-5.7)	5.5 (3.0-not reached)
DCR, % (95% CI)	66.7% (34.3-71.7%)	61.5% (40.6-79.8%)
Median PFS, mo (95% CI)	4.1 (1.5-5.4)	2.7 (1.4-4.4)
PFS rate at 6 mo, % (95% CI)	23.3% (7.5-39.2%)	25.0% (6.8-43.1%)
Median OS, mo (95% CI)	15.1 (10.9-21.7)	
OS rate at 12 mo, % (95% CI)	69.7% (48.9-90.6%)	

[a] Patients evaluated to date.

CI, confidence interval; DCR, disease control rate; DoR, duration of response; OS, overall survival; PFS, progression free survival.

11561 Poster Session

Safety and efficacy of eribulin plus anlotinib in patients with advanced soft tissue sarcoma (ERAS): A multi-center phase II study.

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Background: Both the microtubule-dynamics inhibitor eribulin and the multi-targeted tyrosine kinase inhibitor anlotinib exhibit single-agent anti-tumor activity in previously treated soft tissue sarcoma (STS). This study aimed to evaluate the efficacy and safety of the combination treatment of eribulin and anlotinib in patients with advanced STS. **Methods:** In this multi-center phase II study (ERAS), patients with advanced soft tissue sarcoma who relapsed/progressed after anthracycline chemotherapy or were not candidates for such treatment were included. Patients received eribulin (1.1 mg/m^2 intravenously on days 1 and 8) and anlotinib (12mg orally once daily on days 1-14) every 21 days for 6-8 cycles, followed by anlotinib maintenance. The primary endpoint was progression-free survival rate at 24 weeks (PFR_{24w}). Secondary endpoints included median progression-free survival (mPFS), median overall survival (mOS), objective response rate (ORR), disease control rate (DCR) and safety. **Results:** Thirty-one patients were enrolled. Twenty-eight (90.3%) patients had received anthracycline chemotherapy, and the remaining 3 (9.7%) were chemotherapy-naïve. Pathological types included L-type sarcomas (10 leiomyosarcomas and 6 dedifferentiated liposarcomas) and non-L-type sarcomas (n =15, with 8 subtypes). As of the cut-off date of Jan 28, 2024, the median follow-up time was 30.4 weeks. Response evaluation was feasible in 29 patients. The ORR, DCR and predicted PFR_{24w} were 20.7%, 82.8% and 65.5%, respectively. The mPFS was 30.1 weeks, with no significant difference observed between patients with L-type sarcomas and non-L-type sarcomas. The mOS was not reached. Nineteen (61.3%) patients experienced at least one grade 3/4 adverse event. The most common grade 3/4 adverse events included neutropenia (35.5%), leukopenia (25.8%), hypertension (16.1%), hypertriglyceridemia (16.1%) and increased gamma-glutamyl transpeptidase (16.1%). **Conclusions:** The combination of eribulin and anlotinib shows promising efficacy with an acceptable toxicity profile in patients with advanced STS, irrespective of pathological type. Clinical trial information: ChiCTR2300067650. Research Sponsor: 1·3·5 project for disciplines of excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University.

11562 Poster Session

Anlotinib versus placebo as adjuvant therapy for completely resected high-grade soft tissue sarcomas: Interim results of a phase 2, double-blinded, randomized controlled trial.

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Background: High-grade soft tissue sarcomas (STS) pose a therapeutic challenge due to the high risk of recurrence, even following complete resection. Anlotinib is a multi-targeted tyrosine kinase inhibitor blocking angiogenesis pathways of VEGFR, FGFR, and PDGFR. Given a promising efficacy for treating patients with unresectable advanced STS in previous trials, we evaluated the role of anlotinib as adjuvant therapy for completely resected high-grade STS. **Methods:** In a single-center, double-blinded, randomized, controlled trial, eligible patients were those adults who had not received adjuvant chemotherapy regimens after complete resection of high-grade STS. Patients were randomly assigned in a 1:1 ratio to receive either oral 12 mg anlotinib or placebo once daily on days 1-14 every 3 weeks as a cycle, with up to six cycles until disease recurrence, unmanageable toxicity or death. The primary endpoints included 1-year, 2-year disease-free survival (DFS). **Results:** Between June 2019 and November 2023, 88 patients were randomly assigned to receive anlotinib (n=44) or placebo (n=44). With a median follow-up of 25.99 months at data accrual cutoff on Jan 15, 2024, the 1-year and 2-year DFS rates were 88% and 77% in the anlotinib group, compared to 64% and 58% in the placebo group. Compared to patients in the placebo group, patients in the anlotinib group had a reduced risk of disease recurrence (HR 0.47 [95% CI 0.22~1.00, P= 0.0445]). The median DFS was not reached. Based on tumor histology, the greatest improvement in DFS with anlotinib versus placebo was observed in patients with myxofibrosarcoma (1-year DFS rate: 82% versus 61%; 2-year DFS rate: 64% versus 43%, HR 0.54 [95% CI 0.17~1.65], P= 0.2698) and undifferentiated pleomorphic sarcoma (1-year DFS rate: 86% versus 67%; 2-year DFS rate: 78% versus 67%, HR 0.58 [95% CI 0.12~2.87], P= 0.4971). Thirty-eight patients experienced adverse events (AEs; 34 with grade 1~2, 4 with grade 3): 28 patients (64%) in the anlotinib group versus 10 patients (23%) in the placebo group ($P<0.001$). Three patients discontinued anlotinib, including two for proteinuria/hematuresis (2/44, 5%) and one for secondary poor surgical wound healing (1/44, 2%). **Conclusions:** Current results suggest anlotinib could lower disease recurrence risk in patients with completely resected high-grade STS, with an acceptable toxicity profile. Clinical trial information: NCT03951571. Research Sponsor: None.

	Placebo (n=44)	Anlotinib (n=44)	P
Age (years), median (IQR)	57.5 (50.25~66.00)	56.5 (37.25~65.75)	0.140
Sex, male, n (%)	25 (57)	26 (59)	0.829
Histological type, n (%)			0.466
Myxofibrosarcoma	15 (34)	12 (27)	
Undifferentiated pleomorphic sarcoma	9 (20)	14 (32)	
Others	20 (45)	18 (41)	
DFS, %			
1-year	64	88	
2-year	58	77	
HR (95% CI), anlotinib *vs* placebo	0.47 (0.22~1.00)		0.0445*
Adverse events, any, n (%)	10 (23)	28 (64)	<0.001*

*Statistically significant.

11563 Poster Session

Integrated multi-omics analysis reveals immune landscape of tertiary lymphoid structure in retroperitoneal liposarcoma.

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Background: Retroperitoneal liposarcoma (RPLS) is a rare type of mesenchymal tumor characterized by difficult surgical management, immune desert, poor response to immunotherapy and high local recurrence rate. However, how tertiary lymphoid structures (TLS) dictates complex biological processes such as antitumor immunity remains unknown. Thus, we aimed to investigate the spatio-temporal heterogeneity of TLS formation, maturation, and functional involvement in TIME, and the clinical value of TLS in multiple retrospective RPLS clinical cohorts. **Methods:** 330 patients were retrospectively enrolled into five independent cohorts from the two largest retroperitoneal tumor research centers in China and the TCGA database. Single-cell RNA sequencing (sc-RNA seq) (n=4) and spatial transcriptome seq (n=2) were performed for the estimation of TIME based on treatment-naive RPLS. Transcriptomic profiles of 309 cases in five cohorts were obtained from the ZSFD, GEO, and TCGA databases. TLS was quantified in three different anatomic subregions (intra-tumor, invasion margin and peri-tumor) and correlated with overall survival (OS) and disease-free survival (DFS) by Cox regression and Kaplan-Meier analysis. Multiplex immunohistochemistry (mIHC) was performed to characterize and validate the spatial composition of TLS in another treatment-naive RPLS cohort (n=16), neoadjuvant chemotherapy (n=12) and neoadjuvant radiotherapy (n=20) RPLS cohorts. **Results:** The joint scoring system of T and P scores stratified RPLS into four immune classes with different TLS distribution patterns and prognoses ($p<0.001$). The immune class C-index was significantly higher than the TNM staging system (0.798 vs. 0.62, p=0.005). Importantly, mIHC revealed that regulatory T cells (Tregs) and M2 phenotype tumor-associated macrophages (TAMs) were significantly increased in intra-tumoral TLS in DDLPS compared to WDLPS, showing an immunosuppressive pattern. Strikingly, neoadjuvant chemotherapy and radiotherapy could block this status of immunosuppressive, induced TLS formation and restore the antitumor immune balance with significantly more CD38+IgG+ plasma cells (PCs) in responsive RPLS, whereas non-responsive RPLS deteriorated into a more suppressive one. Sc-RNA Seq and ST analysis further revealed significant intra- and inter-tumoral TIME heterogeneity and identified the underlying transcriptomic programs driving each phenotype. **Conclusions:** Our study provides a high-resolution map of TIME in treatment-naive and neoadjuvant chemotherapy/radiotherapy RPLS. Effective neoadjuvant chemotherapy and radiotherapy can induce TLS formation and restore the antitumor immune balance in RPLS.
Research Sponsor: National Natural Science Foundation of China; 81802302; Scientific Research Project of Shanghai Municipal Health Commission; 20214Y0087, 20204Y0409; "Young Talents" Training Plan of Shanghai TCM-integrated Hospital; RCPY0063; Natural Science Foundation of Fujian province; 2023J011698; Natural Science Foundation of Xiamen City; 3502Z20227279; Hongkou District Clinical Medicine Excellent Young Talents Training Program; HKLCYQ2024-01.

11564 Poster Session

The CT-based multi-omics model for prognostic prediction and tumor microenvironmental alterations in retroperitoneal liposarcoma: A retrospective multicohort analysis.

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Background: Retroperitoneal liposarcomas (RPLS) are tumours with a poor prognosis. Due to the tumour heterogeneity of RPLS, no effective prognostic index has been established. Radiomics has the potential to non-invasively characterize the so-called radiological phenotype of RPLS. We aimed to develop and independently validate a CT-based multi-omics model for predicting prognosis and tumour microenvironment (TIME) in RPLS to guide neoadjuvant therapy in clinical application. **Methods:** In this retrospective multicohort study, we used five independent cohorts of RPLS patients at our centre (n = 173, Zhongshan hospital, Fudan University, China), and the external validation cohort comprising RPLS patients from another medical centre (n = 184, Shanghai Public Health Clinical Center, Fudan University, China), to develop and validate a CT-based multi-omics model predictive of neoadjuvant chemotherapy (n = 10) and radiotherapy (n = 20) response by combining contrast-enhanced CT images and RNA-seq genomic data (n = 59) from tumour samples to assess the immune and metabolic landscape. Using the training dataset, a CT-based radiomics workflow was developed, including manual delineation, sub-segmentation, feature extraction, and predictive model building by LASSO, which was validated according to the area under the curve (AUC) for the internal validation set and external validation set. The clinical-radiomic model was developed through Univariate and Multivariate Cox regression analysis. Kaplan-Meier and log-rank tests were used for the survival analysis. **Results:** A total of 436 patients recruited between September 2009 and October 2021 were included in the training, internal validation, and external validation sets. The OS-related CT-based radiomics models in the training, internal validation, and external validation sets predicted the AUC values of postoperative 5-year OS as 0.71, 0.85, and 0.82, respectively. Strikingly, the clinical-CT radiomics model showed superior prognostic ability in predicting postoperative 5-year OS of 0.83, 0.85, and 0.86. Furthermore, the clinical-CT radiomics risk score was significantly decreased in post-neoadjuvant chemotherapy and radiotherapy with more tertiary lymphoid structures (TLS) and immune cell infiltration, such as plasma cells and B cells, compared to pretreatment. KEGG and ssGSEA analysis further indicated that retinol metabolism was most significantly inhibited in the high clinical-CT radiomics risk score group. **Conclusions:** Our validated clinical-CT radiomics model can predict the prognosis and TIME of RPLS with excellent performance. This may be a promising way to improve prognosis prediction and risk stratification of patients treated with neoadjuvant therapy, when validated by further prospective randomised trials. Research Sponsor: National Natural Science Foundation of China; 81802302; Scientific Research Project of Shanghai Municipal Health Commission; 20214Y0087, 20204Y0409; "Young Talents" Training Plan of Shanghai TCM-integrated Hospital; RCPY0063; Natural Science Foundation of Fujian province; 2023J011698; Natural Science Foundation of Xiamen City; 3502Z20227279; Hongkou District Clinical Medicine Excellent Young Talents Training Program; HKLCYQ2024-01.

11565 Poster Session

A phase II study of the combination of pexidartinib and sirolimus to target tumor-associated macrophages in unresectable malignant peripheral nerve sheath tumors.

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Background: Cytotoxic chemotherapy in patients (pts) with unresectable malignant peripheral nerve sheath tumors (MPNSTs) affords minimal benefit with significant toxicity. Pexidartinib, an inhibitor of colony-stimulating factor-1 receptor (CSF1R), targets infiltrating M2 macrophages which correlate with disease progression; combination with an mTOR inhibitor resulted in sustained tumor control in our xenograft MPNST model. A phase I study of pexidartinib + sirolimus suggested the combination's safety and tumoral static activity where 2 of 6 MPNST pts experienced a progression-free survival (PFS) of >18 weeks. We conducted a phase II study of this combination in pts with unresectable MPNST. **Methods:** This multicenter, single-arm, investigator-initiated phase 2 trial enrolled pts with unresectable MPNST with 0-3 prior systemic therapies, excluding inhibitors of tyrosine kinases or mTOR. Pts were treated with pexidartinib 1000mg and sirolimus 2mg daily. Tumor response was assessed every 6 weeks by RECIST v1.1. With a target sample size of 25 the study had 90% power to detect a difference of 12 weeks in median PFS assuming a 6 week median PFS in historical controls. Exploratory analysis on pre- and on-treatment tumor biopsies included characterization of the tumor immune microenvironment (TIME) by multiplex immunofluorescence and transcriptional analysis. **Results:** Fifteen pts enrolled between 1/1/19 and 1/19/23, 14 initiated therapy and are evaluable, including 4 with Neurofibromatosis Type 1 (NF1) associated MPNST. The study was closed to enrollment on 4/12/23 due to lower-than-expected accruals during the COVID-19 pandemic. Data cutoff was 9/20/23. The median age was 39 years (range 19-72) and 28.6% were female. Ten pts had been on prior systemic therapy (median 1). Twelve pts ceased therapy due to disease progression, one died on treatment from COVID-19 before radiologic evaluation, and one stopped therapy due to rash. The median PFS and median overall survival were 6 weeks (95% CI, 6-19.1) and 21.8 weeks (95% CI, 14.6-NA), respectively. One patient achieved confirmed stable disease. Three pts experienced PFS ≥12 weeks and five pts survived >8 months, four of whom had subsequent therapy. One patient was alive at last follow up after 2.7 years. Therapy was well tolerated with grade 3 treatment-related adverse events occurring in 4 (28.6%) pts, namely leukopenia and rash. Exploratory analyses of paired biopsies performed on 8 pts using multiplex immunofluorescence and bulk RNAseq will be presented. At time of submission, no pts remained on study therapy. **Conclusions:** Cotreatment with pexidartinib and sirolimus has limited efficacy in pts with unresectable MPNST but may benefit a subset of pts. Exploratory analyses of TIME modulation are ongoing. Clinical trial information: NCT02584647. Research Sponsor: FDA; R01FD005745; Plexxikon Inc.

11566 Poster Session

First-in-human CEB-01: Novel loco-regional SN-38 release membrane to prevent local recurrence in retroperitoneal sarcomas.

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Background: Local recurrence after radical surgery (SX) for retroperitoneal soft tissue sarcoma (RPS) occurs in up to 50% of patients and constitutes a major cause of death. CEB-01 is a novel biocompatible and biodegradable membrane implant of poly lactic-co-glycolic acid (PLGA) nanofibers entangled with SN-38 for a steady delivery in the surgical bed after RPS resection. CEB-01 may increase local control rates and survival. **Methods:** This is a multicentre, first in human trial (NCT04619056/EudraCT: 201800102625) following a 3+3 dose escalation design, and an expansion cohort. CEB-01 is implanted after SX at 3 dose levels of SN-38: 9 mg (2 membranes of 180 cm2 at 25 mcg/cm^2), 18 mg, and 36 mg (4 membranes at 25 mcg/cm^2 and 50 mcg/cm^2, respectively). The primary objective was to determine the recommended phase 2 dose (RP2D) level, defined as $<$33% of patients experiencing dose limiting toxicity (DLT) within 2 weeks after SX. DLT is defined as any Grade $\geq$3 toxicity. Secondary endpoints included: efficacy by means of time to local relapse (TTLR), progression-free survival (PFS) evaluated using RECIST 1.1, and overall survival (OS); safety; pharmacokinetics (PK) and quality of life. The study included tumor central pathological review and independent data monitoring committee (IDMC) for efficacy and safety. Here we report the final results for the primary endpoint. **Results:** From Jul 2020 to Nov 2023, 14 patients were included: 10 male; mean age 63 years (range: 39 - 77), 8 with dedifferentiated liposarcoma (LPS), 4 well differentiated LPS, 1 myxoid LPS, and 1 leiomyosarcoma. Post-SX margins were R0 in 82% patients, and R1 in 18%. No dose limiting toxicity (DLT) was observed. RP2D was declared at 18 mg. With a median follow-up of 9.1 months (range: 1-21), no recurrence in the area of the membrane was reported at RP2D and only one patient presented a local recurrence distal to the membrane at 8.5 months after SX. All patients at RP2D were free of distal progressions and alive, with two patients having an OS $>$ 20 months. Adverse events were similar to those post-SX. Grade 3 toxicities reported consisted of 1 patient who experienced retroperitoneal hemorrhage, 1 small intestine obstruction, 1 anemia and 1 fever. Three patients died due to disease progression at the dose level 1; and two at dose level 3, one due to cardiac arrest with bleeding (unrelated to CEB-01), and one due to retroperitoneal hemorrhage (related). SN-38's PK showed dose linearity. At RP2D, the median half-life was 296 hours , C_{max}: 0.75 ng/ml and AUC 0-t: 109 ng/ml*h. Blood levels of SN-38 were detectable 28 days after surgery. **Conclusions:** CEB-01 recommended phase II level is 18 mg. CEB-01 at 18 mg provides promising local disease control and a local steady and prolonged release of SN-38, with a much lower C_{max} than irinotecan. An international phase 2 trial with CEB-01 at 18 mg to demonstrate local control is underway. Clinical trial information: NCT04619056. Research Sponsor: CEBIOTEX S.L.

11567 Poster Session

Do patients with myxofibrosarcoma and undifferentiated pleomorphic sarcoma have different clinical outcomes to immune checkpoint blockade-based therapy?

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Background: Myxofibrosarcoma (MFS) and undifferentiated pleomorphic sarcoma (UPS) are distinct histologic subtypes of soft tissue sarcoma that exist on a spectrum of dedifferentiation. Molecular analyses have found MFS and UPS to be indistinguishable, except for a higher expression of matrix-associated genes in MFS. While immune checkpoint blockade (ICB) is a recognized treatment option for UPS patients according to the National Comprehensive Cancer Network guidelines, clinical outcomes to ICB-based therapy in MFS have not been well described. **Methods:** The objectives of this study were to compare the overall response rate (ORR), progression free survival (PFS), and overall survival (OS) of MFS and UPS patients treated with ICB-based therapy. We retrospectively searched our clinical trial database for MFS and UPS patients treated at our Center with ICB-based therapy. Given the low number of MFS patients identified, we included any MFS patient treated with ICB-based therapy off-label. To determine whether MFS patients treated off-label differed from those treated on a study, a sensitivity analysis was performed comparing PFS and OS between these two groups. Kaplan Meier methods were used to analyze OS and PFS and log rank test was used to compare between groups. ORR were compared using Fisher's exact test. **Results:** A total of 70 patients were included, 43 (61%) with UPS and 27 (39%) with MFS. All UPS patients and 13 MFS patients were treated on one of 8 different clinical trials, two utilized ICB alone and 6 combined ICB with another agent. Eleven of 14 (79%) MFS patients treated off-label received ICB alone; 3 (21%) received ICB plus another agent. Fifty-five patients treated on trials were assessed by RECIST 1.1 (12 MFS and 43 UPS). The median age of MFS patients was higher than UPS (69.5 and 57.2, respectively). Both cohorts were predominantly male (55.6% in MFS and 60.5% in UPS) and had a median of 1 prior line of therapy (range: 0 – 6 in MFS and 0 - 7 in UPS). The median myxoid component of baseline MFS tumors was 30% (range: 10 – 90%). Median PFS and OS (in months) and ORR (%) are outlined (Table). A sensitivity analysis within MFS did not find a significant difference between MFS patients treated off or on a clinical trial. **Conclusions:** In this retrospective analysis, clinical outcomes to ICB-based therapy did not differ between MFS and UPS patients. Based on these data, it may be reasonable to (a) consider ICB as a treatment option for unresectable or metastatic MFS refractory to standard chemotherapy and (b) group UPS and MFS together onto a single cohort in clinical studies of ICB-based therapy. Research Sponsor: None.

	MFS	UPS	P value
Primary analysis			
PFS	4.4 (2.0 – 8.3)	4.1 (1.8 – 5.5)	0.900
OS	17.2 (10.7 – 26.5)	25.5 (15.4 – 35.3)	0.360
ORR	33%	26%	0.716
Sensitivity Analysis			
PFS			
Off-trial	4.4 (1.6 – 8.3)	-	0.495
On-trial	5.3 (1.3 – 14.0)	-	
OS			
Off-trial	16.3 (3.8 – 26.5)	-	0.291
On-trial	22.0 (10.8 – 41.0)	-	

11568 Poster Session

Analysis of the time to progression in patients who underwent metastasectomy plus isolated lung chemoperfusion for disease recurrence after metastasectomy alone.

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Background: The combination of pulmonary metastasectomy (ME) with isolated lung chemoperfusion (ILuP) has shown promising results, however, a direct comparison of the clinical outcomes obtained by ME plus ILuP versus ME alone is complicated. The heterogeneity of patients in terms of cancer types, number of metastases and composition of prior systemic therapy adds to the difficulties of this analysis. **Methods:** Patients who initially received ME alone, and then ME plus normothermic ILuP after the disease relapse, were considered. The aim of the study was to compare the time to pulmonary disease progression (TTP) after the first and second interventions (TTP1 and TTP2, respectively) in the same subjects. **Results:** Of 225 patients who underwent ME plus ILuP in 2007 - 2020, we selected 48 patients who received this treatment due to pulmonary disease progression after ME alone. There were 16 patients with soft tissue sarcoma, 8 patients with osteosarcoma, 14 colorectal cancer cases and 10 patients with other tumor types. The mean number of metastases was 2.94 before ME alone and 4.33 before ME plus ILuP. Cisplatin was used in 30 patients at a mean dose of 191.8 mg, and melphalan was utilized in 18 subjects at a mean dose of 44.1 mg. The median follow-up was 31.1 months. The median TTP1 was 6.9 months, and the median TTP2 was 19.0 months ($p < 0.0001$). TTP2/TTP1 ratio equal or above 1.5 was observed in 34 out of 48 patients (71%). **Conclusions:** This is the first study comparing the results of ILuP plus ME versus ME alone in the same patients. The data obtained strongly support the feasibility of adding isolated lung chemoperfusion to surgery in patients amenable to excision of lung metastases. Research Sponsor: None.

11569 Poster Session

Use of histologic and immunologic factors in sarcoma to predict response rates to immunotherapy.

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Background: Sarcomas are rare mesenchymal neoplasms with substantial histologic and tumor microenvironment heterogeneity, leading to varied treatment responses, particularly to immunotherapy. Because of the heterogeneity of response rates and high risk of disease progression, further determinations of which patients are most likely to benefit from immunotherapy are crucial. In this study, we aim to characterize factors associated with response to immune checkpoint inhibitors (ICIs). **Methods:** 216 patients with advanced sarcoma treated with ICIs between 2016-2023 at Stanford Health Care were analyzed. Overall survival (OS), progression free survival (PFS), objective response rates per RECIST criteria (ORR), and reason for ICI discontinuation were analyzed across histologic subtype, ICI regimen, tumor mutational burden (TMB), and PD-L1. **Results:** The most common histologic subtypes analyzed were leiomyosarcoma (LMS, n=48), liposarcoma (LPS, n=27), and undifferentiated pleomorphic sarcoma (UPS, n=18). Immunotherapy regimens primarily consisted of ipilimumab and nivolumab (77.8%), pembrolizumab (14.8%), and nivolumab monotherapy (6.0%). Median OS for all patients was 12.8 months. Response rates across all sarcomas were complete response (CR) 3.2%, partial response (PR) 13.4%, stable disease (SD) 30%, and progression of disease (PD) 53.2%. The ORR was higher in patients treated with pembrolizumab (21.9%) than with ipilimumab and nivolumab (14.3%). The histologic subtypes with the highest ORR were Kaposi sarcoma (KS, 66.7%), alveolar soft part sarcoma (ASPS, 50%), angiosarcoma (AS, 33.3%), myxofibrosarcoma (MFS, 28.6%), and UPS (27.8%). The subtypes with the lowest ORR were osteosarcoma (OS, 0%), synovial sarcoma (SS, 0%), and LPS (3.7%). The subtypes with the highest median PFS were KS (median not reached, NR), ASPS (NR), MFS (27.3 mo), and UPS (11.3 mo). Overall TMB (n=118) was low with a median of 2 mut/MB. Only 4 patients (3.3%) had a TMB $\geq$10, with a corresponding ORR of 25%. Overall PD-L1 expression (n=93 with TPS or CPS) was also low with a median of 0%. However, positive PD-L1 (n=36/93, $>$ 1%) was associated with better ORR (27.8%, 10/36). 16.2% of patients discontinued immunotherapy due to autoimmune adverse effects; the most common were pneumonitis (18.4%), colitis (15.8%), arthritis (13.2%), and hepatitis (13.2%). **Conclusions:** Response and PFS were highly variable across sarcoma histologic subtype. In this large analysis, KS, ASPS, AS, MFS, and UPS demonstrated the best ORR and longest PFS while OS, SS, and LPS were the lowest. TMB $\geq$10 and PD-L1 expression also correlated with increased ORR. Our findings provide further insight into understanding the sarcoma histologic and immunologic factors that correspond with response to ICIs. Research Sponsor: None.

	CR	PR	SD	PD
KS (n=6)	0.0%	66.7%	0.0%	33.3%
ASPS (n=4)	0.0%	50.0%	25.0%	25.0%
AS (n=15)	6.7%	26.7%	20.0%	46.7%
MFS (n=14)	14.3%	14.3%	35.7%	35.7%
UPS (n=18)	11.1%	16.7%	16.7%	55.6%

11570 Poster Session

Analyzing the effect of treatment modalities on survival in synovial sarcoma.

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Background: Synovial sarcoma (SS) is a rare, slow growing, and aggressive soft tissue sarcoma that commonly affects young adults, with a diagnosis at an average age of 30 years. It usually originates near the joints of the extremities and presents as a painless lump. Metastasis to the regional lymph nodes and lungs is common. SS is proposed to be a result of a chromosomal translocation leading to the fusion of SYT and SSX genes. Standard treatment is tumor resection followed by adjuvant therapy. No study has compared the effects of different surgery and adjuvant therapy types on overall survival. This study will compare the effects of various therapeutic modalities on overall survival for patients with SS. **Methods:** The National Cancer Database (NCDB) was used to identify patients diagnosed with SS from 2004 to 2020 using histology code 9040 as assigned by the Commission on Cancer Accreditation program. Kaplan-Meier, ANOVA Chi-Square, and Logistic Regression tests were performed, and data were analyzed using SPSS version 29. Statistical significance was set at $\alpha = 0.05$. **Results:** The sample retrieved from NCDB consisted of 2566 patients with SS. Of these 2566 patients, 1962 patients (76.5%) received surgery at the primary site. The receipt of surgery was associated with a marked increase in survival (132.2 months vs. 48.6 months, $p<0.001$). Out of the surgical patients, 883 patients (45.0%) received a lobectomy, 696 patients (35.5%) received a wedge segmental resection, 21 patients (1.07%) received an extended lobectomy and 1 patient (0.05%) received a hepatectomy. Patients who underwent lobectomy and wedge/segmental resections had improved outcomes compared to patients who received other types of surgery ($p<0.001$). In addition, 898 patients (45.8%) received adjuvant chemotherapy, 38 patients received adjuvant chemoradiation (1.94%), and 22 patients received adjuvant radiation (1.12%). The receipt of adjuvant chemotherapy was associated with better outcomes than receiving no adjuvant therapy (121.9 months vs. 108.4 months, $p<0.001$). The receipt of adjuvant chemoradiation was also associated with better outcomes than receiving no adjuvant therapy (132.2 months vs. 108.4 months, $p=0.023$). The receipt of adjuvant chemotherapy versus adjuvant chemoradiation is not significantly different in regard to overall survival. **Conclusions:** This study confirms that receiving surgery for SS is associated with markedly increased overall survival. Furthermore, wedge/segmental resections and lobectomies are associated with improved outcomes compared to other types of surgery. Receiving adjuvant therapy is associated with improved outcomes as compared to the receipt of surgery alone. Adjuvant chemotherapy and adjuvant chemoradiation are associated with better outcomes than adjuvant radiation alone. Further studies are needed to understand the factors involved in choosing specific treatment modalities for SS. Research Sponsor: None.

11571 Poster Session

A phase II study of an oncolytic herpes simplex virus 2 and an anti-PD-1 antibody in patients with advanced sarcoma.

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Background: OH2 is an attenuated oncolytic Herpes Simplex-2 Virus expressing GM-CSF. In a phase I/II open-label clinical trial OH2 was safe and efficacious as monotherapy. When combined with HX008, a humanized anti-PD-1 antibody, OH2 demonstrated a disease control rate of 50% in solid tumors (1). Here, we present the efficacy results observed in a sarcoma-specific expansion cohort of the trial. **Methods:** Patients refractory to ≥1 prior line of systemic therapy were allocated to a monotherapy group receiving intratumoral OH2 once every 2 weeks and a combination group receiving i.t. OH2 and HX008 (i.v) every 3 weeks. The primary endpoint was best objective response rate (ORR, per RECIST v 1.1). Secondary endpoints were disease control rate (DCR), progression free survival (PFS), overall survival (OS), duration of response (DOR) and adverse effects (AEs). **Results:** 26 patients were enrolled in the phase II trial, 7 in the monotherapy group and 19 in the combo group. Median age was 52 years, with 65.4% females. 50% had received ≥3 prior lines of therapy, whereas 30.7% had prior lines of immunotherapy. 25 patients were evaluable for efficacy (1 withdrew). ORR was 0% and 16.7%; DCR 14.3% and 50.0%; median PFS 1.4 and 2.1 months, and median OS 4.5 and 22.3 months, for the monotherapy and combo groups, respectively. In the combo group we observed 1 CR and 2 PRs, in which the DOR was 4.2, 5.6 and 11.1 months (Table). Angiosarcoma and fibrosarcoma patients experienced clinical benefit with durable disease control, with one angiosarcoma patient remaining in study for >1 year. Treatment was well tolerated with most common AEs being grade I and II, including GGT elevation (26.9%), fever (23.1%), neutropenia (19.2%), weight loss (15.4%), LDH elevation (15.4%), and anemia (15.4%). **Conclusions:** OH2 and HX008 demonstrated goodsafety and encouraging anti-tumor activity in a phase II sarcoma cohort. Further clinical investigation of this combination is warranted. 1. Zhang et al, 2021; PMID: 33837053. Research Sponsor: None.

Characteristics	OH2 (n=7)	OH2+HX008 (n=19)
Median age (range) (years)	45(25-65)	54(24-69)
Disease status (%)		
Recurrent locally advanced	2(28.6)	9 (47.4)
Distant metastases	5(71.4)	10 (52.6)
Prior treatment (%)		
1-2 lines	2(28.6)	11(57.9)
≥3 lines	5(71.4)	8(42.1)
Prior immunotherapy (%)	2 (28.6)	6 (31.6)
Best ORR overall (%)	0	16.7
Median PFS (months)	1.4 (CI: 1.2-2.8)	2.1 (CI: 1.5-3.1)
Median OS (months)	4.5 (1.9-8.2)	22.3 (8.9-NR*)

*: not reached.

11572 Poster Session

Maintenance treatment with toripalimab and anlotinib after anthracycline-based chemotherapy in patients with advanced soft tissue sarcoma (TORAN): A single-arm, phase 2 trial.

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Background: In patients with advanced soft tissue sarcoma (STS) who have achieved disease control after anthracycline-based chemotherapy, maintenance therapy is being explored. This study evaluated the efficacy and safety of toripalimab (a monoclonal antibody against the programmed cell death-1 receptor) combined with anlotinib (a multitargeted tyrosine kinase inhibitor) as a maintenance treatment. **Methods:** Patients with advanced STS who have achieved disease control after at least four cycles of first-line anthracycline-based chemotherapy were enrolled in this single-arm, phase 2 trial. Fifty patients are planned to receive treatment with toripalimab and anlotinib. The primary endpoint was progression-free survival rate at 24 weeks (PFR_{24w}) during maintenance therapy. Secondary endpoints were median progression-free survival (PFS), median overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety. **Results:** By the cut-off date of Jan 25, 2024, 22 patients were enrolled, including patients with leiomyosarcoma (n =5), synovial sarcoma (n =3), epithelioid sarcoma (n =3), dedifferentiated liposarcoma (n =2) and other different subtypes of sarcomas (n =9). The median follow-up time was 11 months. Response has been evaluated in 18 patients. The ORR and DCR were 22.2% and 100%. The PFR_{24w} was 67%, the median PFS was 11.8 months, and the median OS was not reached. The grade 3 or higher adverse events were hypertension (n =4), hemorrhage (n =1), adrenal insufficiency (n =1) and hypertriglyceridemia (n =1). **Conclusions:** Maintenance therapy with toripalimab and anlotinib is a promising treatment option for patients with advanced STS after first-line anthracycline-based chemotherapy. Clinical trial information: ChiCTR2100054901. Research Sponsor: 1·3·5 project for disciplines of excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University.

11573 Poster Session

Active surveillance in patients with extra-abdominal desmoid-type fibromatosis: A combined analysis of three prospective observational studies.

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Background: Three observational studies on active surveillance (AS) in patients with extra-abdominal desmoid-type fibromatosis (DTF) provided prospective evidence supporting AS as frontline approach. Identification of prognostic factors for failure of AS will help determine the appropriate treatment strategy. The aim of this study was to confirm previous findings and investigate the prognostic impact of clinical and molecular variables on a larger series. **Methods:** Data available on January 31st 2024 from 3 prospective observational studies in Italy, the Netherlands and France in which DTF patients were followed for ≥3 years during an initial AS approach were merged. Patients ≥18 years, with primary extra-abdominal sporadic DTF (abdominal wall, extremity, head & neck, trunk) and with *CTNNB1* mutation (T41A, S45F, S45P, WT, "other") available were eligible for the analyses. The primary study endpoint was treatment-free survival (TFS). Secondary endpoints included incidence of RECIST progression, spontaneous RECIST regression and regression post-RECIST progression. **Results:** Two hundred and eighty-two patients (n= 282) with median follow up of 53 months (IQ, 39-63) were included. Three-year and five-year TFS and crude cumulative incidences (CCI) of RECIST progression, RECIST regression and regression post-RECIST progression were 69% (64-75%) and 66% (61-73), 34% (95% CI 28-40) and 35% (30-41), 26% (95% CI 21-32) and 34% (29-41), and 35% (95% CI 26-47) and 40% (30-52), respectively. Larger initial tumour size (P=0.031), *CTNNB1* mutation (S45F and "other" mutation P=0.049), and head/neck and extremity tumour locations (P=0.032) were associated with worse TFS at multivariable analysis (Table 1). Consistently smaller size and abdominal wall were associated with higher probability of initial spontaneous RECIST regression and a specular trend for mutation was also seen (Table). **Conclusions:** This study confirms that spontaneous regression occurs in a significant proportion of patients and two third are treatment free at 5 years. Initial size, *CTNNB1* mutation and location should be factored in the initial decision-making process. Research Sponsor: None.

	Treatment-Free Survival			RECIST Regression		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Sex			0.586			
Male vs Female	1.17	(0.67-2.02)		1.02	(0.52-1.98)	0.956
Age at diagnosis (years)	0.80	(0.57-1.11)	0.396	1.05	(0.74-1.50)	0.467
Initial tumor size (mm)	2.43	(1.20-4.90)	0.031	0.48	(0.27-0.84)	0.004
CTNNB1 mutation types			0.049			0.401
T41A vs S45P	1.62	(0.69-3.81)		0.88	(0.50-1.55)	
S45F vs S45P	2.01	(0.79-5.11)		0.45	(0.17-1.15)	
Other vs S45P	4.72	(1.54-14.48)		0.56	(0.20-1.59)	
Wild type vs S45P	1.35	(0.46-3.95)		0.70	(0.33-1.49)	
Tumour localization			0.032			0.014
Extremities vs Abdominal wall	1.56	(0.85-2.86)		0.29	(0.13-0.66)	
Head and neck vs Abdominal wall	3.83	(1.54-9.51)		0.45	(0.11-1.79)	
Trunk vs Abdominal wall	1.38	(0.76-2.51)		0.58	(0.33-1.01)	

11574 Poster Session

Prognostic significance of plasma circulating tumor DNA fraction in patients with advanced sarcoma: A French Sarcoma Group study.

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Background: The integration of liquid biopsies into clinical guidelines is revolutionizing the management of late-stage cancer. A notable advancement is the use of broad genomic analysis of circulating tumor DNA (ctDNA) for quantifying tumor fraction (TF). While TF's prognostic relevance in carcinomas has been explored, its significance in sarcomas remains unclear. **Methods:** This study involved patients with advanced sarcomas from two precision medicine studies (BIP, Institut Bergonié, Bordeaux, France; STING, Gustave Roussy, Villejuif, France) across two French Sarcoma Group sites. All participating patients underwent comprehensive genomic profiling with the FDA approved FoundationOne Liquid CDx assay. TF was measured using single-nucleotide polymorphism-based aneuploidy analysis as previously described (Reichert et al. 2023). Progression-free survival (PFS) and overall survival (OS) were assessed from treatment commencement (PFS) or the date of ctDNA profiling (OS) to disease progression, death, or last patient contact. Univariate analysis examined variables such as age, gender, tumor grade, metastatic sites, performance status (PS), and prior treatment lines. **Results:** 195 patients (103 males, 92 females) entered the study. The three most frequent histological subtypes were leiomyosarcomas, dedifferentiated liposarcomas, and undifferentiated pleiomorphic sarcomas. Median age was 56 (range 18-91). Thirty patients (15.4%) had high TF ($\geq$ 10%). Among the 189 patients who underwent systemic treatment post-ctDNA profiling, elevated TF correlated with significantly poorer PFS (2.6 vs 4.3 months, p=0.018) and OS (6.7 vs 14.1 months, p=0.005). Multivariate analysis identified TF and ECOG performance status as independent predictors of OS. **Conclusions:** Plasma ctDNA TF is a practical and independent prognostic biomarker in advanced sarcoma patients. Its integration into treatment paradigms can facilitate precision therapeutic strategies tailored to individual tumor biology. Research Sponsor: None.

11575 Poster Session

Intimal sarcomas (ISarc) of the cardiac chambers (CC) of the heart and great vessels (GV): A comprehensive genomic profiling (CGP) study.

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Background: ISarc of the CC and GV are extremely rare primary tumors of the cardiac chambers (CC), aortic root (AO) and pulmonary artery (PA). These tumors are rarely resectable and are associated with rapid progression and poor clinical outcome. We queried whether CGP could uncover new routes to targeted therapies for this aggressive form of malignancy. **Methods:** 27 cases of ISarc were centrally reviewed and required direct association with the intimal surfaces of the CC and GV with supporting routine histologic features and immunohistochemical staining patterns. DNA and RNA extracted from the ISarc cases were both sequenced using a hybrid-capture based CGP to study all classes of genomic alterations (GA) and determine MSI status, TMB level, HRD score, genomic ancestry, cosmic trinucleotide signature (Signature) and germline status. PD-L1 expression was measured by IHC (Dako 22C3 and TPS scoring). **Results:** The 27 ISarc cases included 15 CC and 12 GV (11 pulmonary artery ISarc and 1 aortic root Isarc). There were 24 (88.9%) histologic grade 3 and 3 (11.1%) grade 2 tumors. Median ages for all ISarc ranged from 45 to 46 years and were similar in both groups. The CC ISarc pts tended to be female when compared with the GV pts (73% vs 50%; P=.26). GA potentially impacting targeted therapy selection in clinical trials for rare tumors included amplifications of *MDM2* in 66.7% of CC ISarc and 50% of GV ISarc, *PDGFRA* in 53.3% CC and 41.7% of GV; homozygous deletions in *CDKN2A* in 26.7% in CC vs 66.7% of GV was near significant (p=0.055) and significantly more frequent point mutations in *PIK3CA*in CC at 20% vs 0% in GV (p=.007) and *ERBB3* in 13.3% of CV and 8.3% of GV which was not significant. EUR ancestry was present in slightly more than 50% of ISarc cases and similar in both sub-groups. Median TMB was similar and ranged from 4.3 to 4.7 mutations/Mb with 1 (6.7%) CC ISarc having a TMB of $>$ 10 mut/Mb. 1/5 (20%) tested ISarc cases stained for low level PD-L1 expression. **Conclusions:** CGP of ISarc cases reveals that these tumors do feature a modest number of GA potentially associated with benefit for targeted therapies but low and absent biomarkers predictive of immunotherapy benefit. Further study of ISarc in a setting of rare tumor clinical trials appears warranted. Research Sponsor: None.

	All ISarc	CC ISarc	GV ISarc	CC vs GV P value
Number of Cases	27	15	12	27
Gender (% Female)	63% F	73% F	50% F	=.26
Median Age (range)	46 (30-74)	45 (36-74)	46 (30-72)	NS
EUR Ancestry	55.6%	53.3%	58.3%	NS
Germline GA	*VHL* & *KEAP1*in 1 case	None	*VHL* & *KEAP1*in 1 case	NS
CDKN2A	48.1%	26.7%	66.7%	=.05
MDM2	59.3%	66.7%	50.0%	NS
PDGFRA	48.1%	53.3%	41.7%	NS
CDK4	51.9%	60.0%	33.3%	NS
KIT	40.7%	40.0%	33.3%	NS
PIK3CA	11.1%	20.0%	0%	=.007
ERBB3	11.1%	13.3%	8.3%	NS
MSI High Status	0%	0%	0%	NS
Mean gLOH/HRD+ Status			12.9%/1/8 (12.5%)	
TMB > 10 mutations/Mb	3.7% (Median 4.0)	6.7% (Median 4.0)	0% (Median 4.3)	
PD-L1 + (>1% TPS staining	1/5 (20%)	0% (0/5)	20% (1/5)	

11577 Poster Session

Seven year update on SOC-1702: A phase 2 study using trabectedin (T) in combination with ipilimumab (I), nivolumab (N) and trabectedin (T) in previously untreated patients with advanced soft tissue sarcoma.

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Background: Advanced soft tissue sarcoma is most often associated with a fatal outcome. This report is an update on the results of the SOC-1702 Phase 2 study for previously untreated STS. **Methods:** Objectives, Primary: Evaluate best response rate by RECIST v1.1; Secondary: Assess progression-free survival (PFS) at 6 months and overall survival. Patients and Methods: Eligible patients for this Phase 2 study are males or females ≥ 18 years of age with locally advanced unresectable or metastatic soft tissue sarcoma, previously untreated, with measurable disease by RECIST v1.1. Treatment protocol: (I) 1 mg/kg i.v. q 12 wks, (N) 3 mg/kg i.v. q 2 wks, (T) 1.2 mg/m2 CIV q 3 wks. **Results:** Efficacy: Ninety-one patients were evaluated for efficacy. These subjects completed at least two treatment cycles and had at least one follow-up CT scan. The best responses were 9CR, 14PR, 54SD and 14PD with 25% ORR, 85% DCR. PFS rate at 6 months was 56%; Median PFS was 7.4 (95% CI: 5.6-9.2) months; Median OS was 32.0 (95% CI: 19.8-44.2) months. The best responders (CR and PR) were patients with LMS, UPS, LPS, synovial sarcoma, myxofibrosarcoma, endometrial stromal sarcoma, clear cell sarcoma, DSRCT, and chondrosarcoma. Notably, out of the 91 patients who participated in the study between 2017 and 2022, 23 (25%) patients are still alive as of January 1, 2024, the data cut-off date. Safety: Grade 3/4 TRAEs related to Trabectedin include both hematologic and non-hematologic toxicities: fatigue, nausea, vomiting, fever, exhaustion, dehydration, asthenia, cellulitis of port, anemia, neutropenia, thrombocytopenia, transaminitis, elevated CK. There were no hematologic toxicities related to Nivolumab or Ipilimumab. Grade 3/4 TRAEs include decreased TSH, increased T4, increased TSH, transaminitis, hyponatremia, dehydration, pruritus, and psoriasis. **Conclusions:** Taken together we have confirmed that (1) Trabectedin in combination with Ipilimumab and Nivolumab is a safe and effective regimen for previously untreated advanced STS, and (2) Randomized studies are needed to confirm whether this regimen is superior to standard first line therapy for advanced soft tissue sarcoma. Clinical trial information: NCT03138161. Research Sponsor: None.

11578 Poster Session

A signal-finding study of nivolumab and relatlimab in patients with advanced chordoma.

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Background: Chordomas are derived from notochordal remnants and are typically treated with surgery and radiation therapy. For advanced chordomas, there are no approved systemic therapies. Preclinical evidence and anecdotal reports have indicated that the immune system is active in chordomas and that there may be a role for immunomodulation in treating this disease. **Methods:** This study is a single-arm, signal-finding trial in patients with advanced chordoma treated with the anti PD-1 antibody nivolumab (480 mg Q4 weeks up to 2 years) and the anti-LAG3 antibody relatlimab (160 mg Q4 weeks up to 2 years). The primary objective of this study was to assess the safety of nivolumab and relatlimab in subjects with progressive metastatic or locally advanced/unresectable chordoma. Secondary objectives were to ascertain the median progression free survival (PFS), response rate (RR), and the 4- and 6-month PFS by RECIST 1.1. **Results:** Out of a planned enrollment of 20 patients, 10 patients (8 Male, 2 Female) were consented and treated on trial. Enrolled patients had the following sites of involvement: 5 clival/c-spine, 4 sacral, and 1 thoracic. Nine had conventional subtype chordoma and 1 had chondroid subtype. Eight of the 10 patients had previous surgery, 6 had previous radiation therapy and 5 had 1-2 lines of prior systemic therapy, including one who received pembrolizumab. Pretreatment biopsies were obtained from 9 out of 10 patients and blood has been collected on all patients. Nine patients were evaluable for study outcomes. A total of 64 AEs (Grades 1-4) have been noted to date, with 6 events being classified as grade 3-4: nausea, facial pain, headache, and pulmonary embolism. Five serious adverse events (SAEs) were noted in patients on treatment: headache (2), asthma (1), myocarditis (1), and sepsis (1). The median PFS of the 9 evaluable patients was 21.4 weeks. At 4 months, 7 out of 9 patients were progression free (77.7%). At 6 months, 4 out of 9 patients remained progression free (44.4%) and had continued progression-free survival at 1 year. One out of 9 (9.1%) patients had a PR via RECIST 1.1. One patient discontinued treatment due to an adverse event (grade 1 myocarditis). **Conclusions:** This signal-finding study indicated that some patients with advanced chordomas can receive benefit with relatlimab in combination with nivolumab. The combination was well-tolerated and no new safety signals were found in this rare patient population. Correlative studies are ongoing. The study was closed for slow accrual. Clinical trial information: NCT03623854. Research Sponsor: Bristol Myers Squibb.

11579 Poster Session

Patient-reported global health to predict adverse health outcomes in an expanded cohort of patients with advanced sarcoma.

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Background: The rarity of sarcoma cancers and the debilitating effects of chemotherapy often lead to challenges in the quality of life for these patients. Uncontrolled symptoms can cause unplanned hospital admissions and emergency room visits that delay treatment regimens and negatively impact patient outcomes. To assess patients' physical and mental well-being during treatment, we used validated tools like the PROMIS Global Health v1.2 (PROMIS-10) surveys. We sought to expand our cohort of patients with advanced sarcoma to better understand and establish the relationship between PROMIS-10 scores and adverse outcomes of interest, including unplanned admissions/ER visits and patient mortality. This is one of the largest quality of life assessments published for patients with sarcoma. **Methods:** All patients seen in the Sarcoma Clinics at The Ohio State University routinely complete the PROMIS-10 survey at each clinic visit. For this expanded cohort, we collected the raw and normalized t-scores for PROMIS-10 surveys for all patients consented to The Ohio State University Sarcoma Registry (OSU-14242) from 2/1/2020 to 12/31/2022. We also collected data on unplanned hospital admission/ED visits and mortality data for each patient. **Results:** A total of 1598 surveys for 332 patients were collected for the study period. Our prior cohort was 112 patients. Most patients were female (54%), and the median age was 58 years. Seventy-two of 332 patients experienced an unplanned admission or ED visit during the study, with a total of 137 such encounters during the study period. Physical and Mental PROMIS-10 scores were significantly associated with an unplanned admission or ED visit ($p < 0.001$), a stronger correlation compared to our initial cohort, where we did not find a correlation with Mental PROMIS-10 scores. Physical and Mental PROMIS10 scores were independently analyzed as they were highly collinear. A total of 82 patients died during the study period. There was no association found between PROMIS-10 scores and mortality in a mixed model; however, bivariate associations did reveal that patients who had died had reported lower Physical and Mental PROMIS-10 scores. We had previously seen a signal that female patients had higher mortality rates, but with a larger sample size, there was no correlation between female gender or age with unplanned hospital admission/ED visits and mortality. **Conclusions:** Our research consistently shows that obtaining patient-reported outcomes during treatment is essential to accurately evaluate patients' physical and mental well-being. We are currently performing an additional confirmatory analysis of the predictive value of the PROMIS-10 survey for adverse events and treatment-related complications with a larger sample size. This data is paramount in developing more effective interventions to significantly improve patients' quality of life. Research Sponsor: None.

11581 Poster Session

Fragility index analysis of systemic therapy clinical trials in soft tissue sarcoma (STS).

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Background: The fragility index (FI) measures the robustness of randomized clinical trials (RCT) that have positive results based on statistical p-values. It estimates the minimum number of events that are needed to reverse the trial results from positive to negative. Here, we perform FI analysis on RCTs evaluating systemic treatments for STS. **Methods:** A systematic search of the Medline and Embase databases for RCTs in adults with advanced STS (Jan 1998 to Dec 2023) was conducted. Gastrointestinal stromal tumor trials were excluded. The FI framework was adapted to allow the use of time-to-event (TTE) outcomes – progression-free survival (PFS) or overall survival (OS) as previously described (Desnoyers et al 2021). Survival tables were reconstructed from published data on positive TTE outcomes, using the Parmar Toolkit. Positive secondary endpoints were used only if the primary endpoint was negative. The number of additional events that would result in a non-significant effect for the hazard ratio (HR) of the positive endpoint of each trial (FI) was calculated and expressed as a proportion of the size of the experimental arm (fragility quotient; FQ). The number of censored patients – those who withdrew consent or were lost to follow-up (C_n) was noted. **Results:** Among 47 RCTs, 16 (8 phase II; 8 phase III) trials had positive outcomes. The primary endpoint was positive and used for FI analysis in 11/16 trials (68.8%). PFS was the most common positive outcome, evaluated in 13 trials (81.3%). The median FI was 6 (range 2 – 52), with FI $<$ 10 observed in 11 trials (68.8%). Median FQ was 7% (range 1 – 59%) and 10 trials (62.5%) had FQ $<$ 10%. Among 14 trials that reported data, C_n was $\geq$ FI in 7 trials (50%). Only 2 of 4 trials (50%) that led to regulatory approval had FI $>$ 10 or FQ $>$ 10%. Of the other 2, one drug approval was subsequently withdrawn (Table). **Conclusions:** Most positive clinical trials in STS were fragile and their outcomes may be confounded by the level of censoring. Real-world evaluation of approved systemic therapies and value scales such as ESMO Magnitude of Clinical Benefit scale or ASCO value framework are needed to confirm clinical benefit of systemic treatments in STS. Research Sponsor: None.

STS trials that led to regulatory approval.

PMID	Treatment	Control	Population	Endpoint	n	HR	p-Value	C_n	FI	FQ
27291997	Doxorubicin + Olaratumab $^{\beta}$	Doxorubicin	Any STS	OS	133	0.46	0.0003	7	7	9%
22595799	Pazopanib	Placebo	Non-adipocytic STS	PFS $^{\alpha}$	369	0.31	$<$0.0001	12	38	15%
28854066	Eribulin	Dacarbazine	Liposarcoma	OS $^{\alpha}$	71	0.51	$<$0.001	NR	4	6%
26371143	Trabectedin	Dacarbazine	Liposarcoma or Leiomyosarcoma	PFS	518	0.55	$<$0.001	22	52	15%

α: Outcome was the primary endpoint. β: Withdrawn following negative phase III trial. NR: not reported.

11582 Poster Session

Primary localized malignant PEComa treated with surgery: A report of a large series of patients treated in a referral institution.

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Background: Perivascular Epithelioid Cell Tumors (PEComa) are mesenchymal neoplasms with a characteristic myomelanocytic immunophenotype. These tumors exhibit a broad anatomic distribution, and aggressive clinical behavior has been correlated with histological features such as tumor size and increasing mitotic activity. PEComas arising from the kidney are referred to as angiomyolipomas and usually lack metastatic potential, whereas epithelioid angiomyolipomas do have metastatic potential. Until now, only case reports or a limited number of patients have been documented in the literature, resulting in a lack of data regarding their clinical behavior. In this study, we present the outcomes of a large series of patients (pts) with primary localized malignant PEComa. **Methods:** This is a retrospective study involving all consecutive pts of any age affected by primary and localized malignant Pecoma surgically treated with curative intent at our institution from January 2000 to December 2023. Eligible pts had a pathologically confirmed diagnosis of malignant Pecoma. We present the outcome results in terms of Disease-Free Survival (that includes Local Recurrence (LR), Distant Metastases (DM), or death as first events) and Overall Survival (OS). Due to the low number of events only univariable analyses were performed. **Results:** 48 patients (19/48 M; 29/48 F) were identified. Median age at surgery was 50 yrs (range 18-80). Primary site was extremity and trunk in 19/48 pts, retroperitoneum in 13/48 pts and other in 16/48; median size of tumor was 11 cm (range 1-30 cm). At a m-FU of 57 mos (IQR:22-116), 8 pts died. Five- and 10-yr OS was 81.6% [95% Confidence Interval (CI): 70.1-94.9%)] and 77.3% (CI: 64.2-93.0%), respectively. One patient developed LR as first event, 9 developed DM and 3 died without any LR and DM; 3 and 1 patients developed DM as 2^{nd} and 3^{rd} event, respectively. Five- and 10-yr DFS was 69.4% [CI: 56.3-85.6%] and 65.1% (CI: 50.9-83.1%). Predictors of higher risk of DFS were age (>64 yrs old) and site of origin [p=0.5; HR trunk and arms: 1.2 (CI: 0.38-3.81) vs. retroperitoneum and 3.49 (CI: 0.43-28.37) vs other]. **Conclusions:** In this series PEComas have a 30% risk of recurrence at 5 years. While age and the site of origin are associated with the natural history of the disease, better pathologic criteria are needed to stratify their risk. Research Sponsor: None.

11583 Poster Session

Systemic therapy in NF-1 associated malignant peripheral nerve sheath tumors (MPNST).

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Background: MPNST are rare sarcomas that have a poor prognosis and are challenging to treat. Around 50% of MPNSTs are associated with NF1, 40% are sporadic, and 10% are radiation-associated. Doxorubicin (D) based chemotherapy (CT) regimens are commonly used in the front-line, and combinations have better response rates than single agents. Response to second-line regimens is not well documented. The objective of this study is to document efficacy of systemic regimens in MPNST as a benchmark for future novel therapeutics in this space. **Methods:** 72 patients (pts) with NF1-associated MPNSTs in an MD Anderson database were reviewed retrospectively from EMR. Variables collected included demographics, primary MPNST location, localized vs metastatic, and treatments received (+/- radiation, +/-surgery, +/- lines of CT). Responses (progressive disease (PD), stable disease (SD), partial response (PR)) as interpreted by treating physician and radiology reports and time on treatment for 1st and 2nd line chemotherapy regimens were assessed. Cox proportional-hazard regression was used to investigate associations of variables with overall survival (OS: from time of diagnosis to death or last follow-up). **Results:** Demographic and CT details are provided (Table). The median age at diagnosis was 34.5 yrs (range: 9-71). The most common MPNST location was the trunk (56.94%). D based regimens were the most frequent 1st-line CT (65.7%), and gemcitabine- docetaxel was the most frequent 2nd-line CT (33.3%). In pts with metastases, 74.4% got 1st line, 44.7% 2nd line, 25.5% 3rd line, and 12.7% got 4th line therapy. Median follow-up was 2.46 yrs (IQR 1.24-9.52). The median time on treatment for 1st and 2nd line CT was 110 (IQR 48-153) and 57 (IQR 41-133) days, respectively. In the multivariate COX model for the entire cohort, male sex (HR: 0.35, 95%CI: 0.18-0.68), lower extremity primary (HR: 0.09, 95%CI: 0.02-0.40), and absence of metastases at last follow up (HR: 0.05, 95%CI: 0.02-0.17) were associated with decreased risk of death. Additional analysis on efficacy and survival of the systemic therapy regimens will be presented at the meeting. **Conclusions:** In this study < 50% pts with advanced NF1 related MPNST made it to 2nd line CT and outcomes were inferior to the predominantly D based 1st line regimens. This highlights an area of high unmet need. Research Sponsor: None.

	Total n = 72	% of Total
Sex		
Male	38	52.78
Female	34	47.22
Primary		
Cervical	6	8.33
Lower Extremity	12	16.67
Trunk	41	56.94
Upper Extremity	9	12.5
Head & Neck	4	5.56
Metastasis		
At diagnosis	3	4.2
Subsequent	44	61.1
None	25	34.7
Neoadjuvant CT		
Y	15	20.83
N	57	79.17
Radiation		
Y	45	62.5
N	27	37.5
Surgery		
Y	57	79.2
N	15	20.8
1st Line CT (n = 35)		
D based*	23	65.7
No D**	12	34.3
Response in 1st Line (n=35)		
PR	2	5.7
SD	20	57.1
PD	13	37.1
2nd Line CT (n = 21)		
D based*	5	23.8
No D**	16	76.2
Response in 2nd Line (n=21)		
PR	1	4.8
SD	9	42.9
PD	11	52.4

D based: D/ D+ Ifos/VDC/ D+DTIC/ VDC-IE No D: Gem-Doce/IE/Carbo/Rapamycin/Tipifarnib-sorafenib/bevacizumab.

11584 Poster Session

Off-label use of fam-trastuzumab deruxtecan-nxki with early activity in a cohort of patients with desmoplastic small round cell tumor.

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Background: Desmoplastic small round cell tumor (DSRCT) is a rare and aggressive sarcoma occurring predominantly in pediatric, adolescent and young adult biologic males, and is molecularly characterized by the pathognomonic EWSR1-WT1 fusion. Despite aggressive multi-modality therapy outcomes for those with DSRCT remain poor, and more effective therapies are urgently required. Prior pre-clinical data and transcriptomic analyses of DSRCT patients has suggested the relevance of the ERBB2 pathway in this disease, prompting the off-label use of fam-trastuzumab deruxtecan-nxki (T-DXd) in the treatment of patients of DSRCT patient with relapsed and refractory disease. **Methods:** Patients with relapsed/refractory DSRCT received T-DXd 5.4 mg/kg intravenously in 21-day cycles. Whole body PET and CT of the chest, abdomen and pelvis were used for monitoring. Response was correlated with HER2 immuno-histochemistry (IHC) status and transcriptomic analysis by RNA sequencing (RNAseq) when available. **Results:** Seven patients received the agent, and at the time of submission 3 patients had at least one follow up imaging test after receiving between 6 and 9 cycles of T-DXd. Treatment was overall well tolerated with the only grade 3 toxicity of transaminitis (in patients with known liver metastases), which self-resolved. All other toxicities including constipation, nausea, and fatigue were grade 2 or less. All 3 patients have experienced clinical benefit including one patient with a RECIST 1.1 partial response and two patients with stable disease. Additionally, favorable responses were noted by PET imaging. Four additional patients with relapsed/refractory DSRCT have initiated off-label treatment with T-DXd and are pending imaging responses. 7/7 and 4/7 patients have available IHC and ERBB2 RNA expression data available respectively. All ERBB2 RNA expression data is elevated when compared with the median across all evaluated pediatric tumors in our institutional series. **Conclusions:** The use of anti-HER2 therapy in a limited and unselected group of heavily pre-treated DSRCT patients is demonstrating an early signal of activity with minimal toxicity and suggests that formal assessment as monotherapy or in other relevant combinations in clinical trials is warranted. Further correlation with IHC and RNAseq expression data may help optimize correlatives and/or generate biomarkers for future clinical trials. Research Sponsor: None.

11585 Poster Session

Sorafenib treatment duration in desmoid tumors.

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Background: Desmoid tumors are soft-tissue neoplasms, which, although unable to metastasize, can cause significant morbidity due to local invasion. Currently, the first-line approach is active surveillance. For tumors that progress during surveillance, systemic therapies can be used, including nirogacestat, sorafenib, pazopanib, and cytotoxic chemotherapy. However, their optimal duration is unknown. Here, we aim to assess the risk of treatment failure after discontinuing sorafenib before one year. **Methods:** We analyzed all patients with desmoid tumors treated with sorafenib at three academic centers from 01/01/2000-12/01/2021. We included patients who discontinued sorafenib not due to radiological or clinical progression and had documented no intention to start the next line of therapy at the time of discontinuation. The primary endpoint was 2-year treatment-free survival between patients who stopped sorafenib before and after 1 year. The secondary endpoint was the rate of toxic effects recorded according to the Common Terminology Criteria for Adverse Events during treatment. We calculated treatment-free survival using the Kaplan-Meier method with the Log-Rank Test to estimate the 95% confidence interval. All patients were censored at the 2-year mark. Fischer's Exact T-test was performed to assess between-group differences. **Results:** 40 patients received sorafenib and discontinued it with no intention to start a next line of therapy. The main reasons for discontinuation were side effects (n=21, 52%) and physician-patient preference (n=10, 25%). 27 (67%)were women, and median age at diagnosis was 36.Regarding race and ethnicity,27 (47%)were White, 8 (20%)were Black, and 16 (40%) were Latino. The tumor was in the lower extremity in 10 (25%) cases, trunk in 3 (7%) cases, abdominal wall in 10 (25%), intra-abdominal in 5 (12%), upper extremity in 5 (12%) head-neck in 1 and breast in 1. 20 patients stopped treatment before one year and 20 after one year, with 7 and 3 patients requiring a next line of therapy in each group, respectively. The 2-year treatment-free survival was 60% (95% confidence interval [CI], 0.35 to 0.85) in the prior to 1-year group and 87.5% (95% CI, 0.71 to 1.0) in the post-1-year group (P = 0.046). The most frequently reported adverse events while on sorafenib were grade 1 or 2 events of palmar-plantar erythrodysesthesia (40%) and diarrhea (40%), with no difference between groups on therapy discontinuation due to side effects (p=0.1). **Conclusions:** Discontinuing sorafenib prior to 1 year was associated with a higher risk of requiring further therapy within the following two years. Still, most patients did not require additional therapy. This finding underscores the complexity of determining the optimal duration for sorafenib therapy, and multiple features should be considered, including side effects, symptom improvement, fertility planning, tumor cellularity (evaluated by T2 MRI signal), and physician-patient shared decision. Research Sponsor: None.

TPS11586 Poster Session

A first-in-human phase 1 trial of T cell membrane-anchored tumor targeted IL12 (ATTIL12) -T cell therapy in advanced/metastatic soft tissue and bone sarcoma.

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Background: Interleukin-12 (IL12) is a cytokine that induces antitumor immune response and immune memory by activation of NK cells, induction of IFNg, and maturation of DC cells in the tumor microenvironment (TME). However, prior clinical experience with IL12 has been limited by toxicities including cytokine release syndrome (CRS) and hepatotoxicity. We developed a novel tumor-targeted IL12 gene (ttIL12) that encodes the p35 and p40 VNTANST fusion subunits that targets cell surface vimentin (CSV). Vimentin is expressed intracellularly in many normal and neoplastic mesenchymal cells but our group discovered that intracellular vimentin is often flipped to the cell surface (referred to as CSV) across multiple tumor types.2 Preclinical studies demonstrated efficacy and induction of long-term memory of ttIL12 against metastatic osteosarcoma with reduced toxicity in immune competent models.3 However, ttIL12 had limited efficacy in treating large volume tumors and did not completely eliminate toxic peripheral cytokines. To address this, our team generated a membrane anchored ttIL12 to arm T cells known as attIL12-T cell therapy. We hypothesize attIL12 will minimize toxic cytokines in peripheral tissues but promote induction of INFg/TNFa in the TME to decrease the toxicity and boost efficacy. **Methods:** This is a phase 1 trial of attIL12-T cells in patients (pts) with locally advanced or metastatic soft tissue or bone sarcomas to assess safety, maximal tolerated dose (MTD) and recommended phase 2 dose (RP2D). Pts in part A (dose finding) will be enrolled using a Bayesian optimal interval (BOIN) design in up to 6 dose levels. Part B (dose expansion) will evaluate preliminary efficacy in 10 additional pts with osteosarcoma treated at the RP2D. Treatment:Pts will undergo leukapheresis to collect peripheral blood mononuclear cells (PBMCs) for generation of attIl12-T cells. Bridging therapy is permitted but not required. Pts will receive cyclophosphamide (Cy) IV prior to planned T cell administration. attIL12 T cells will be administered at the specified dose level IV in a single infusion (dose level 1 and 2) or 2 serial doses (dose level 3-6) on day 0 and day 14. Pts will be monitored for toxicity and response evaluation. Pts will also undergo pre-treatment/on-treatment tumor biopsies for translational and correlative analysis. Eligibility:Pts must be $\geq$ 12 years of age, have a confirmed diagnosis of locally advanced or metastatic sarcoma, evaluable disease, received at least 1 prior line of standard systemic therapy, ECOG PS 0-1, and adequate organ function to tolerate immune-effector cell therapy. Pts with known sensitivity to Cy, active/prior autoimmune disease, uncontrolled CNS disease, or other uncontrolled comorbidities that pose potential safety risk will be excluded. Enrollment to cohort 1 began in Dec 2023. Clinical trial information: NCT05621668. Research Sponsor: American Cancer Society; SRA-22-194-01-SRA.

TPS11587 Poster Session

DCC-3116 in combination with ripretinib for patients with advanced gastrointestinal stromal tumor: A phase 1/2 study.

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Background: Advanced cancers driven by mutations at or downstream of receptor tyrosine kinases (RTKs), including *KIT*- and *PDGFRA*-mutant gastrointestinal stromal tumor (GIST), activate autophagy as an escape mechanism in response to RTK pathway inhibitors. ULK1/2 kinases are key regulators that initiate autophagy in response to stress, such as KIT/PDGFRA inhibition in *KIT*- and *PDGFRA*-mutant GIST. Therefore, ULK1/2 inhibition represents a potential targeted approach to selectively inhibit autophagy and is an attractive strategy for combination with RTK pathway inhibitors, including ripretinib. Ripretinib is a switch-control KIT/PDGFRA tyrosine kinase inhibitor approved as a ≥fourth-line therapy for advanced GIST. In the INTRIGUE trial, ripretinib demonstrated comparable efficacy and more favorable safety compared with sunitinib in second-line advanced GIST. DCC-3116 is an investigational, selective, potent, switch-control kinase inhibitor of ULK1/2 in development for combination with targeted therapies that activate autophagy, such as ripretinib. In a GIST xenograft model, animals treated with ripretinib demonstrated stable tumor burden while treatment with ripretinib + DCC-3116 resulted in complete regressions. Here, we describe the design of a phase 1/2, multicenter, open-label study evaluating the safety, recommended phase 2 dose (RP2D), and preliminary efficacy of DCC-3116 in combination with ripretinib in advanced GIST (NCT05957367). **Methods:** This phase 1/2 study includes safety/dose-finding (part 1) and expansion (part 2). In part 1, patients (pts) ≥18 years must have pathologically confirmed GIST with a *KIT* or *PDGFRA* mutation and disease progression on or intolerance to ≥1 systemic regimen. Escalating doses of DCC-3116 will be assessed with ripretinib 150 mg once daily. Part 1 will use safety, pharmacokinetics, pharmacodynamics, preliminary efficacy, and a Bayesian optimal interval design to identify the RP2D for part 2 and the maximum tolerated dose. In part 2, second-line pts with confirmed GIST with a *KIT* exon 11 mutation and disease progression on or intolerance to first-line imatinib will be enrolled. Part 2 will use a two-stage design with non-binding futility and efficacy analyses after stage 1 to explore efficacy of the combination dose selected in part 1. Exclusion criteria for both parts include use of other anticancer treatments, such as ripretinib, and any investigational therapies within 14 days, use of moderate or strong inhibitors or inducers of cytochrome P450 3A4 or P-glycoprotein, symptomatic central nervous system metastases or leptomeningeal disease, and active infections. Primary objectives in part 1 are to identify adverse events and the RP2D. The primary objective of part 2 is to determine the objective response rate per modified Response Evaluation Criteria in Solid Tumors version 1.1. The study is currently enrolling. Clinical trial information: NCT05957367. Research Sponsor: Deciphera Pharmaceuticals, LLC.

TPS11588 Poster Session

Peak study: A phase 3, randomized, open-label multi-center clinical study of bezuclastinib (CGT9486) and sunitinib combination versus sunitinib in patients with gastrointestinal stromal tumors (GIST).

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Background: Imatinib is the worldwide standard for first-line therapy of advanced KIT-mutant GIST. However, secondary resistance mutations in the KIT ATP-binding domain (exons 13, 14), activation loop (exons 17, 18), or both develop and result in loss of imatinib-sensitivity. Bezuclastinib has a highly selective inhibition profile, leading to minimal off-target toxicities and allowing for combination with sunitinib. While no single tyrosine kinase inhibitor (TKI) inhibits all KIT mutations, the combination of bezuclastinib + sunitinib targets commonly occurring primary (exons 9, 11) and secondary (exons 13, 14, 17, and 18) KIT mutations and may provide more durable responses. The early signs of clinical activity, tolerability, and safety observed with the combination thus far in Peak Part 1 (Somaiah et al. [presentation] CTOS 2023. Paper 62) are consistent with the completed Phase 1/2 study (PLX121-01). **Methods:** Peak (NCT05208047) is a global, randomized, open-label, multi-part Phase 3 study evaluating the efficacy and safety of bezuclastinib + sunitinib versus sunitinib as second-line treatment in adult pts who were intolerant to imatinib or whose tumors had imatinib-resistance. Current Peak study sites are located in North America (3 countries), South America (3 countries), Europe (12 countries), and Asia-Pacific (4 countries). The lead-in portion to test a new formulation of bezuclastinib, (Part 1) completed enrollment in April 2023. Based upon PK and safety, a dose of bezuclastinib 600 mg QD + sunitinib 37.5 mg QD was determined for Part 2 of the Peak study. Part 2 will enroll ~388 pts to be randomized (1:1) to bezuclastinib 600 mg QD + sunitinib 37.5 mg QD or sunitinib 37.5 mg QD alone. Key inclusion: >1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (mRECIST) v1.1, Eastern Cooperative Oncology Group Performance Status 0-2, adequate organ function, and prior imatinib therapy (no other prior therapy). Key exclusion: known PDGFR mutations or succinate dehydrogenase deficiency, clinically significant cardiac disease, and use of strong CYP3A4 inhibitors or inducers. The primary endpoint is progression-free survival (PFS) confirmed by blinded independent central review per mRECIST v1.1. Additional efficacy (including overall survival and objective response rate) and safety endpoints will be evaluated and circulating tumor DNA (ctDNA) will be collected and assessed. Clinical trial information: NCT05208047. Research Sponsor: Cogent Biosciences, Inc.

TPS11589 **Poster Session**

Randomized phase III trial of neo-adjuvant and adjuvant chemotherapy vs adjuvant chemotherapy alone for localized soft tissue sarcoma (NACLESS, JCOG2102).

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Background: Soft-tissue sarcomas (STS) are a rare malignant tumor. Adjuvant perioperative chemotherapy has been investigated for high-risk patients due to the poor overall survival (OS) for surgery. A meta-analysis revealed that adjuvant chemotherapy (AC) with doxorubicin plus ifosfamide (AI) significantly prolonged OS with an absolute risk reduction of 11%. However, the optimal timing for surgery and number of courses of chemotherapy are still controversial. In Europe, Italian sarcoma group and the Spanish sarcoma group reported on the non-inferiority of three courses of neoadjuvant chemotherapy (NAC) + surgery without AC, compared to three courses of NAC + surgery + two courses of AC. On the other hand, even in the same Europe, the latest report on perioperative chemotherapy with AI from Germany was a trial of surgery + AC. Furthermore, adjuvant chemotherapy itself remains skeptical in other countries such as the US, UK, and Canada. No investigation has been made into whether chemotherapy/surgery are better to initiate treatment with. In Japan, the standard treatment is three courses of NAC with AI, surgery, and two of AC with AI. However, in JCOG1306, NAC was discontinued in 12 of 70 (17.1%) patients due to high toxicity. Only one patient (1.4%) became partial response after NAC, whereas six patients (8.6%) had disease progression during NAC. Of the 65 patients eligible for limb-sparing surgery at enrollment, three (4.6%) underwent limb amputation. Upfront surgery followed by three courses of AC was considered the most promising treatment, it avoided extended surgery and reduced toxicity while maintaining an OS equivalent to the standard treatment. The aim of this trial is to optimize the balance between the survival benefit of perioperative chemotherapy, reduce toxicities, and risks of extended surgery. **Methods:** This is a multicenter two-arm open-label randomized phase III trial. Patients are randomly assigned to standard (three courses of NAC, surgery, and two of AC) or experimental (surgery and three courses of AC) arms with AI comprising doxorubicin (30 mg/m^2, days 1, 2) and ifosfamide (2 g/m^2, days 1–5). Major inclusion criteria were (1) spindle cell STS; (2) T2-4N0M0 (UICC/AJCC 8th edition) and deeply located; (3) resectable tumors in the extremities or trunk; (4) age, 16–70 years; (5) ECOG performance status of 0–1; (6) no history of chemotherapy/radiotherapy; and (7) sufficient bone marrow function. To evaluates the non-inferiority in OS (margin: hazard ratio of 1.61) with power of 70% and one-sided alpha of 10%, 224 patients will be enrolled from 39 institutions in Japan. We began this study on November 16, 2022, and 27 of 224 patients have been enrolled as of January 7, 2024. Clinical trial information: jRCTs031220446. Research Sponsor: National Cancer Center Japan.

TPS11590 Poster Session

Randomized controlled, open-label, phase IIb/III study of lurbinectedin in combination with doxorubicin versus doxorubicin alone as first-line treatment in patients with metastatic leiomyosarcoma.

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Background: Lurbinectedin (LUR) is a synthetic chemical entity structurally related to trabectedin that inhibits oncogenic transcription and is active in tumors addicted to transcription. Synergistic activity of the combination of LUR with Doxorubicin (DOX) was found in solid tumors. Preliminary results from two trials showed efficacy for LUR/DOX in anthracycline-naïve advanced Leiomyosarcoma (LMS) (1^{st} or 2^{nd} line) at different doses. In a phase 2 trial in soft tissue sarcoma (STS) patients (pts) (mostly with LMS: 12/20 pts), a combination of DOX 50 mg/m^2 + LUR 2 mg/m^2 Day (D)1 q3wk resulted in a response rate (RR) of 35% (4/7 LMS pts responding) and a disease control rate (DCR) at 24 wks of 40% (1). A phase 1b/2 trial in 10 advanced STS pts found a RR of 60% (5 were LMS, with 3 partial responses) treated at DOX 25 mg/m^2 D1 or D1,D8 + LUR 3.2 mg/m^2 D1 q3wk, (2). The promising results of these trials provide a rationale for further exploring this combination in a phase 2b/3 trial as first-line therapy for metastatic LMS (SaLuDo - NCT06088290). **Methods:** SaLuDo is a randomized, open-label study evaluating LUR in combination with DOX compared to DOX alone as first-line treatment of pts with metastatic LMS. The primary endpoint is progression-free survival (PFS) according to Independent Radiological committee (IRC). Secondary endpoints include overall survival, PFS according to Investigator assessment (IA), overall response rate, duration of response, and clinical benefit rate (according to IRC and IA), safety profile, patient-reported outcomes, pharmacokinetics, and exploratory pharmacogenomic analysis. Main inclusion criteria include age $\geq$ 18 years, confirmed diagnosis of metastatic LMS, and no prior systemic treatment for metastatic disease. Exclusion criteria include prior treatment with anthracyclines, lurbinectedin or trabectedin. The phase 2b part of the study will randomize approximately 120 pts into 3 arms (1:1:1): Control arm (DOX 75 mg/m^2 D1 q3wk; experimental ARM A (DOX 50 mg/m^2 D1 + LUR 2.2 mg/m^2 D1 + 1ry GCSF prophylaxis q3wk), and experimental ARM B (DOX 25 mg/m^2 D1 + LUR 3.2mg/m^2 D1 + 1ry GCSF prophylaxis q3wk). Stratification will be done according to site of primary tumor (uterine vs. soft tissue), sites of metastatic disease (lung as unique site vs. other) and time from diagnosis to study entry ($\leq$ 12 months vs. >12 months). One of the two experimental arms will be dropped out at the end of phase 2b. The study will then enter the phase 3 part and approximately 120 pts will be randomized 1:1 between the control arm and the selected experimental arm. An Independent Data Monitoring Committee will oversee the conduct of the study. The first patient was randomized in 09/2023. The phase 2b part of the study is ongoing and recruiting patients in Europe and the USA. 1. Cote EJC 2020; 126:21-32. 2. Cote. JCO 2023; 41: Abst 11507. Clinical trial information: NCT06088290. Research Sponsor: None.

TPS11591 Poster Session

A phase I/II trial of neoadjuvant pegylated arginine deiminase (ADI-PEG 20) with ifosfamide and radiotherapy in soft tissue sarcomas (STS) of the trunk or extremity.

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Background: Outcomes for the treatment of metastatic STS remain poor. Better therapies are needed for local and distant control. Arginine is essential to neoplastic growth, yet up to 88% of STS do not express argininosuccinate synthetase (ASS1), an enzyme necessary to produce arginine. ADI-PEG 20 is a microbial enzyme that degrades arginine causing auxotrophy in cancer cells that are ASS1 negative. Pre-clinical data demonstrates that arginine deprivation shunts glutamine towards oxidation via the TCA cycle, thus depleting glutathione stores and increasing oxidative stress to the cell. We hypothesize that the combination of ADI-PEG 20, ifosfamide, and radiation therapy can potentiate cellular death. The encouraging safety and clinical data from the ADI-PEG 20 + radiation + temozolomide trial (NCT04587830) further support this combination. We are conducting a phase I/II trial examining the safety and tolerability to determine the recommended phase II dose (R2PD) and evaluate the efficacy of ADI-PEG 20 in combination with ifosfamide and radiation in patients with high-grade STS.
Methods: Eligible patients include untreated intermediate or high-grade extremity or truncal STS planned for definitive resection with performance status 0-1 and adequate organ function. Metastatic disease is exclusionary as well as receiving prior treatment for the study cancer. The total number of patients to be enrolled is approximately 35. Up to 15 patients will be enrolled in the phase I portion with a 3 + 3 dose escalation design with ADI-PEG 20 in combination with escalating doses of ifosfamide and radiation. The primary objectives include determining safety and tolerability as well as the recommended phase II dose (RP2D). Patients will be treated neoadjuvantly with ADI-PEG 20 dosed once weekly starting on Cycle 1 Day -7 with ifosfamide for up to three cycles in combination with standard radiotherapy given over approximately 5 weeks. Ifosfamide will be administered on Days 1 - 5 of all 3 cycles. The phase II participants will receive the combination with ifosfamide at the RP2D determined during phase I. The primary objective of the phase II portion is to determine the percent necrosis and pathologic complete response (pCR) at the time of resection. These endpoints will be summarized by proportions along with the associated 2-sided exact 95% CIs. Assuming the true pCR rate is 25%, enrolling 20 patients will result in a 90% CI for estimating the pCR (10%, 45%). The trial has begun accrual and is soon to open at multiple sites. Clinical trial information: NCT05813327. Research Sponsor: Polaris.