10000 Oral Abstract Session

Association of immunotherapy of high-risk neuroblastoma patients with long term infusion of dinutuximab beta with survival over short term infusion: Results from the HR-NBL1/SIOPEN trial.

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Background: Dinutuximab beta (DB) delivered as long-term infusion is associated with a lower frequency and magnitude of side effects compared to short-term infusion (STI). Here, we evaluated the efficacy (event free survival- and cumulative incidence of relapse-rates at 5 years) of LTI compared to STI within the HR-NBL1/SIOPEN trial (EudraCT:2006-001489-17). **Methods:** High-risk patients as defined by metastatic disease (stage M) or local stage with MYC-N amplification received high intensity induction, surgery, high dose therapy with busulfan/melphalan followed by autologous stem cell transplantation (HDT/SCT) and local radiotherapy. Patients who achieved at least a partial response prior to HDT/SCT within equal or less than 9 months between diagnosis and HDT/SCT without progression were randomized to receive 5 cycles of 100 mg/m^2 DB per cycle either as STI (20 mg/m^2 per day as 8 h infusion; days 1-5) with or without subcutaneous interleukin-2 (scIL2) (6×10^6 IU/m^2 per day; days 1-5 and days 8-12) (R2 randomization) or as LTI (10 mg/m^2 per day as 24h infusion; days 1-10) (d8-17) $\pm$ 3x10^6 IU/m^2 scIL2 (d1-5; d8, d10, d12, d14, d16) (R4 randomization). All patients received 160 mg/m^2 oral isotretinoin (d19-32). **Results:** From 2009-2018, 705 patients (pts) from 18 countries were randomized and eligible for this analysis. The median follow-up time is7.7 years. Key patient characteristics were age 1.5-5yrs: 65% (460 pts), disease status before HDCT: CR 56% (396 pts) versus non-CR 38% (268 pts), MYC-N amplification (MNA): 43% (304 pts); >1 metastatic compartment (MC): 78% (553 pts); time between diagnosis to DB treatment start: $>$ 9 months 48% (302 pts). There were no significantly different patient characteristics between STI and LTI cohorts, except for time to DB start $>$ 9 months: 59% in the LTI cohort vs. 37% in STI.The 5yr EFS was 0.65$\pm$0.03 for LTI vs. 0.56$\pm$0.03 for STI (p = 0.041). The cumulative incidence of relapse was 0.33$\pm$0.03 for LTI vs. 0.42$\pm$0.03 for STI (p = 0.034). Multivariable pseudovalue-regression analysis for 5-year EFS found a significantly worse outcome for stage 4 patients with $>$1MC (p = 0.025; cHR = 1,97), $<$ CR (p = 0.059; cHR = 1.32) and for STI (p = 0.044; cHR = 0.74). **Conclusions:** We previously reported that LTI of DB increased the safety profile (less pain and inflammation) (Lancet Oncol 2018;19(12):1617-1629; J Clin Oncol 37, 2019 (suppl; abstr 10013). Here we demonstrate that LTI is also associated with an improved outcome. Clinical trial information: 2006-001489-17. Research Sponsor: None.

10001 Oral Abstract Session

A phase 2 randomized study of chemoimmunotherapy with or without eflornithine (DFMO) in relapsed/refractory neuroblastoma: A Children's Oncology Group (COG) report.

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Background: Dinutuximab, irinotecan, temozolomide and GM-CSF (DIT) is widely used in first relapsed/ refractory high-risk neuroblastoma (r/r HRNB), however <50% of patients (pts) respond. ODC1 is a key enzyme important for NB cell survival. Difluoromethylornithine (DFMO) irreversibly inhibits ODC1, suppressing polyamine biosynthesis and driving anti-NB activity. DFMO also inhibits arginase and may enhance immunotherapy in r/r NB. COG ANBL1821 was a randomized phase 2 study for pts with r/r NB that evaluated response to DIT with or without DFMO (NCT03794349). **Methods:** Patients with first episode of r/r NB were randomized 1:1 to DIT (Arm A) or DIT with DFMO (6750 mg/m^2 divided TID; Arm B). They were stratified by measurable/evaluable disease, *MYCN* status, prior anti-GD2 therapy, and prior DFMO therapy. Cycles were 21 days. On Arm B, DFMO was initially given continuously; discontinuous DFMO dosing (days 1-7 and 15-21) was instituted due to ototoxicity in the initial cohort. Objective Response Rate [(ORR); sum of complete (CR), partial (PR), and minor (MR) responses per the 2017 International Neuroblastoma Response Criteria (INRC)] was determined based on central review of imaging. Toxicities were graded per CTCAE v5.0. **Results:** 91 eligible and evaluable pts (44 Arm A, 47 Arm B) were randomized May 2019-Jan 2024. 28/44 (63.6%) of Arm A pts and 32/47 (68.1%) of Arm B pts had relapsed or progressive disease (RPD); the remaining pts had refractory disease. The ORR was 61.4% (27/44) for Arm A and 57.4% (27/47) for Arm B (p=0.566). On Arm A, 22/44 (50%) achieved CR or PR compared to 23/27 (48.9%) on Arm B. Response rates for pts with RPD were similar to those with refractory disease in both arms. The 1-year progression-free survival (PFS) for Arm A was 70.0±8.0% and 56.8±8.2% for Arm B. Overall survival was 87.0±5.7% and 81.4±6.3% for Arms A and B, respectively. The most common toxicities reported on both arms were hematologic and gastrointestinal. Fewer pts on Arm B (n=7) had Grade 3+ pain than on Arm A (n=15) (p=0.0326). Hearing loss was a toxicity of interest; with continuous dosing, 55.6% (5/9) of Arm B pts developed hearing loss requiring DFMO dose hold. With discontinuous dosing, hearing loss was 15.8% (6/38) on Arm B compared to 6.3% (2/32) on Arm A (p=0.275). 14/16 (87.5%) NB+ marrows were GD2+ at enrollment; loss of GD2 was not detected on persisting NB cells in on therapy marrows analyzed. **Conclusions:** The addition of DFMO to DIT did not improve response rates in pts with first r/r HRNB, though the response rates in both arms confirmed DIT activity in this population. The ORR to DIT is higher than previously reported, likely due to use of the 2017 INRC that includes MR in calculation of ORR. Rates of CR+PR in this trial were similar to those previously reported. DFMO was associated with an increased incidence of hearing loss which was partially mitigated by discontinuous dosing. Clinical trial information: NCT03794349. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA180886; National Cancer Institute/ U.S. National Institutes of Health; U10CA180899.

10002 Oral Abstract Session

Vincristine and topotecan versus carboplatin-, etoposide-, and vincristine-based chemotherapy for ocular salvage in group D and group E intraocular retinoblastoma: A randomized, comparative trial.

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Background: India has the highest burden of retinoblastoma worldwide. The access to Intra-arterial chemotherapy is limited and systemic chemotherapy remains the standard of care in low-middle income countries(LMIC) like India. There is a need to find alternative systemic chemotherapy due to growing concerns of long-term toxicities with standard Carboplatin and Etoposide based therapy. Topotecan is an attractive option as it is devoid of late toxicities and found to be effective in retinoblastoma. However, the data is very limited. **Methods:** We did a randomised comparative trial in children with group D/E intraocular retinoblastoma (IORB) to compare 2 different chemotherapy regimens. Between October 2021 and March 2023, participants fulfilling the inclusion criteria were randomised to receive either vincristine, topotecan(VT-arm) or high dose carboplatin, etoposide, and vincristine(HDCEV-arm) chemotherapy every 3-weekly for 6 cycles with focal therapy after 2-cycles. The reassessment was done every two cycles.The primary objective was to compare the treatment failure rates at the end of 6-cycles, which was defined as need for non-protocol therapy, enucleation or external beam radiotherapy(EBRT). The secondary objectives were to compare final globe salvage rates (which includes all forms of therapy except EBRT) and toxicities. **Results:** Forty(42 eyes) newly diagnosed cases with group D/E IORB were enrolled. Out of which 19 children(20 eyes) received VT and 21(22 eyes) received HDCEV- based regimen. Baseline parameters were comparable in both arms. After a median follow up of 12.4 months (range, 5.7-22.6), the treatment failure rate was significantly less in HDCEV-arm compared to VT-arm (45.5% vs 75%,HR-2.64, 95% CI, 1.13-6.13, p = 0.02). The 24 months enucleation free-survival was 54.5% in HDCEV-arm and 35% in VT-arm ($p < 0.01$). There were no deaths in any arm and both treatments were tolerated well. However, the incidence of febrile neutropenia (73.6% vs 43%, p = 0.05) and episodes of grade 3/4 diarrhoea (13 vs 4,p = 0.02) was more in VT-arm compared to HDCEV-arm.The response after 4-cycles was comparable with 90% and 85% showing partial response in HDCEV and VT-arm respectively(p = 0.92) but this effect could not be sustained in VT-arm. **Conclusions:** Administration of Topotecan is feasible even in LMIC setting without therapeutic drug with manageable toxicity in children. VT is inferior to HDCEV in globe salvage and has slightly more toxicity. The initial response achieved with VT could not be translated into globe salvage. There is a need to find alternative therapy and the combination of VT with carboplatin can be an attractive option. Clinical trial information: 2021/09/047121. Research Sponsor: None.

10003 Oral Abstract Session

Safety and efficacy of the EZH1/2 inhibitor valemetostat tosylate (DS-3201b) in pediatric patients with malignant solid tumors (NCCH1904): A multicenter phase I trial.

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Background: Valemetostat tosylate (DS-3201b; valemetostat) is a first-in-class dual inhibitor targeting the epigenetic regulators EZH1 and EZH2. In Japan, valemetostat has been approved for the treatment of r/r adult T-cell leukemia/lymphoma and peripheral T-cell lymphoma. These enzymes are implicated in tumors characterized by SMARCB1/INI1 deficiencies, such as malignant rhabdoid tumors or epithelioid sarcoma, which frequently occur during childhood and adolescence. Valemetostat is expected to show antitumor activity against such malignancies. **Methods:** This open-label, multicenter phase I trial evaluated the safety, efficacy, and recommended phase 2 dose (RP2D) of valemetostat in pediatric patients with malignant solid tumors. Valemetostat was administered orally once daily in 28-day cycles. The dose-escalation phase used a 3 + 3 design, testing three dose levels (150, 200, and 250 mg/1.7 m^2). Following RP2D determination, 15 patients were enrolled in the expansion cohort. The primary endpoint was dose-limiting toxicity (DLT) incidence in the dose-escalation cohort. **Results:** Between March 2020 and January 2023, 30 pediatric patients were enrolled (median age: 8 yr; range: 3–19 yr). Among these, 13 (43.3%) patients were INI1-negative by immunohistochemistry. Diagnoses included atypical teratoid/rhabdoid tumor (AT/RT, *n* = 6), malignant rhabdoid tumor (*n* = 1), neuroblastoma (NB, *n* = 8), and chordoma (*n* = 3). No DLTs were observed among 12 evaluable patients, and 250 mg/1.7 m^2 was established as the RP2D. Common grade >3 adverse events included lymphocytopenia (26.7%), neutropenia (26.7%), and anemia (16.7%). Notable treatment-related adverse events included grade 3 pneumocystis pneumonia (*n* = 1, 3.3%) and pneumonitis (*n* = 2, 6.7%). One patient with NB developed acute lymphocytic leukemia as a secondary malignancy. Pharmacokinetic analysis revealed no significant differences in T_{max} and T1/2 compared with the phase II study in Japanese adults (J201 study); however, C_{max} and AUC_{tau} were lower within the range of variation in adults. Objective response was observed in two of 14 patients (14.2%) with measurable disease, both with AT/RT. Long-term disease control exceeding 1 yr were noted in NB (*n* = 2), chordoma (*n* = 1), rhabdoid tumors (AT/RT; *n* = 1), and glioma (*n* = 1). **Conclusions:** Valemetostat was safe in Japanese pediatric patients, demonstrating antitumor activity against INI1-negative tumors, such as AT/RT. These findings support further exploration of valemetosat in combination therapies targeting SMARCB1/INI1-deficient tumors. Additionally, the durable control of tumor observed in NB suggests potential efficacy of valemetostat against this malignancy. This study was supported by the Japan Agency for Medical Research and Development and Daiichi Sankyo Co., Ltd. Clinical trial information: jRCT2031190268. Research Sponsor: Japan Agency for Medical Research and Development.

10004 Oral Abstract Session

Alectinib in children and adolescents with solid or CNS tumors harboring ALK-fusions: A data update from the iMATRIX alectinib phase I/II open-label, multi-center study.

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Background: Alectinib is a next generation oral inhibitor of ALK-fusion proteins, being investigated in children and adolescents with ALK-fusion bearing tumors at diagnosis or relapse. Here we present updated safety and efficacy data from the iMATRIX Alectinib phase I-II study (NCT04774718). **Methods:** Patients, less than 18 years of age, with ALK fusion-positive solid or CNS tumors for whom prior treatment had proven to be ineffective or for whom there was no satisfactory treatment available were eligible. Patients were recruited to Part 1 to confirm the recommended phase 2 dose (RP2D) and to monitor drug pharmacokinetics. Investigators reported Best Overall Response according to RANO (CNS tumors) or RECIST v1.1 (solid tumors) criteria with a data cut off of July 2024. **Results:** In total 22 patients with a median age of 8 years were enrolled. Fourteen patients were diagnosed with solid tumors: inflammatory myofibroblastic tumor (n = 9), renal cell carcinoma (n = 2), mesothelioma (n = 1), nephroblastoma (n = 1), and atypical melanocytic tumor (n = 1). Six patients were diagnosed with CNS tumors: high grade glioma (n = 5) and pleomorphic xanthoastrocytoma (n = 1). Two patients had ineligible conditions: histiocytosis (n = 1) and anaplastic large cell lymphoma (n = 1). Among the 22 patients, 14 had not received prior systemic therapy. ALK fusion partners were EML4 and CLTC in 3 patients, TPM3 and KIF5C in 2 patients, and DCTN1, FN1, KIF5B, NPM, PPP1CB, STRN, CLIP1, RANBP2, ZEB2, PLEKHA7, CDC42BPB and HNRNPA3 in 1 patient each. In the 21 safety evaluable patients, only 1 DLT of Grade 3 increased alanine aminotransferase, in the context of multiple viral infections, was reported. The DLT resolved after treatment interruption and Alectinib was restarted at a reduced dose level, and then tolerated well. Eighteen patients (86%) experienced at least one Adverse Event (AE) reported as related to Alectinib, the majority being of Grade 1 and 2 severity. Grade $\geq$ 3 AEs related to alectinib were reported for 5 patients (23.8%) and there were 2 patients with serious AEs related to Alectinib. There were no new safety signals detected. Investigator reported Best Overall Response rate in 16 patients was 87.5%; (14 PRs) and 2 patients were reported to have stable disease. A partial response was observed in 5/5 evaluable patients with CNS tumors and in 9/11 evaluable patients with solid tumours. Six patients were excluded from the efficacy analysis due to ineligible tumor type (n = 2), not dosed (n = 1), no measurable disease according to RANO criteria (n = 1) or lack of response assessment by the analysis cut-off date (n = 2). **Conclusions:** Alectinib continues to have a favourable safety profile in pediatric patients. Despite this being a very challenging population to treat, clinical efficacy results are transformational with the majority of patients experiencing a tumor response. Clinical trial information: NCT04774718. Research Sponsor: Hoffmann-La Roche.

10005 Oral Abstract Session

Results of a phase II trial of olaparib in combination with ceralasertib in patients with recurrent and unresectable osteosarcoma.

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Background: Osteosarcoma is the most common bone tumor of children, adolescents, and young adults and patients with recurrent osteosarcoma have very poor outcomes. The observed response to cisplatin in osteosarcoma, in vitro susceptibility of osteosarcoma cell lines to ATR and PARP inhibitors, and the presence of mutations in genes involved in DDR served as the basis for the development of this trial. **Methods:** In this single arm, open label phase II trial of olaparib and ceralasertib patients aged 12-40 weighing > 40 Kg with recurrent osteosarcoma and measurable unresectable disease were eligible for Cohort 1. The primary endpoint for Cohort 1 was event-free status at 4-months. Secondary endpoints included objective response rate (ORR) and event-free survival (EFS). After an early study amendment changing the dosing strategy based on clinical data generated from other trials, patients received Olaparib 150mg twice a day on days 1-28 and ceralasertib 80mg twice a day on days 1-14 of a 28-day cycle. Using a two-stage design and a planned sample size of 34 evaluable Cohort 1 patients receiving the amended dosing strategy there is 90% power to detect a 20% increase (39% vs 19%, selected based on a historical benchmark) in the proportion of patients who are event-free at 4-months. Interim analysis required ≥2 of 15 patients to be 4-months event-free to proceed to Stage 2; at Stage 2, ≥11 of 34 patients 4-months event-free for evidence of efficacy. **Results:** The study proceeded to full accrual based on the interim analysis. As of 1/21/2025 data-cut off, 38 patients from four centers were enrolled in Cohort 1 between November 2020 and November 2024; 37 were eligible and evaluable for safety, objective response, and survival analyses. Excluding four patients enrolled before the study amendment updating dosing, 33 patients were evaluable for the primary objective. Median age was 19.6 years (range 12.7-38.2). Patients received an average of 4.2 (range 1-9) prior therapy regimens, including 26 (70%) patients with prior multi-tyrosine kinase inhibitor treatment. Four of the 33 evaluable were event-free at 4-months (12%; 95% CI: 4%-29%). One of 37 patients had an objective response (ORR: 2.7%; 95% CI: 0.14%-16%). The 4-month EFS±SE was 13.5±5.6% (n = 37). The most common ≥ grade 3 adverse events were platelet count decreased and anemia (38% and 27%, respectively). **Conclusions:** The study did not meet the predetermined threshold for efficacy for Cohort 1; however, a subset of patients may be benefit from this combination treatment. Results of Cohort 2 (resectable osteosarcoma limited to the lung parenchyma) will be reported separately. Assessment of potential biomarkers of response is underway. Clinical trial information: NCT04417062. Research Sponsor: The Osteosarcoma Institute; AstraZeneca.

10006 Oral Abstract Session

Phase II assessment of carboplatin with etoposide and high-dose ifosfamide in rEECur, an international randomised controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES).

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Background: rEECur, the first randomised controlled trial (RCT) in RR-ES, has previously defined high dose ifosfamide (IFOS) as the most effective regimen in this setting compared to gemcitabine-docetaxel, irinotecan-temozolomide and topotecan-cyclophosphamide. Platinum drugs show activity in RR-ES and are frequently given with etoposide in this setting. **Methods:** Patients aged at least 2 years with RR-ES were randomised to 3-week cycles of either IFOS 15 g/m^2 by continuous intravenous (IV) infusion over 5 days or IV carboplatin 400 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1 to 3 (CE). Primary outcome was event-free survival time (EFS). Secondary outcomes included overall survival time (OS), toxicity and quality of life (QoL). A probability-based Bayesian approach was used. **Results:** 139 patients recruited between 22/03/21 and 28/05/24, were randomised 1:1 to IFOS (n = 69) or CE (70). Median age was 18 years (range 3-59). Patients had refractory disease (14%), 1st recurrence (81%), $>$ 1strecurrence (6%). Sites of progression were primary site only (21%), pleuropulmonary metastases only (24%), and other or combined metastatic disease (55%). More CE patients had baseline GFR $<$ 90 ml/min/1.73m^2(41% versus 23%). Median follow-up (reverse Kaplan-Meier) was 18 months (mos). Median EFS was 5.1 mos (95% CI 3.1, 6.3) for IFOS and 3.5 mos (95% CI 2.5, 6.1) for CE. Median OS was 14.4 mos (95% CI 11.5, 20.7) for IFOS and 19.0 mos (95% CI 11.2, 24.6) for CE. Given the observed data the posterior probabilities that EFS and OS were better after IFOS than after CE (ie Pr[true hazard ratio $>$ 1 | data]) were 87% and 55% respectively. Grade 3+ adverse events present in $>$ 5% of patients randomised to IFOS (left hand values) compared with CE were febrile neutropenia (30% v 10%), anaemia (9% v 9%) and thrombocytopenia (3% v 7%). Acute kidney injury was present in 2% v 0% and encephalopathy in 5% v 0%. There were no measurable differences in QoL. **Conclusions:** There was insufficient evidence of efficacy with CE compared to IFOS to continue recruitment to phase III in this first RCT of a platinum-etoposide combination in RR-ES. IFOS remains the most effective regimen in this disease setting. The trial remains open, comparing IFOS with and without the tyrosine kinase inhibitor lenvatinib. Funded by Cancer Research UK (C22436/A28028, CTUQQR-Dec22/100006, A28474). Clinical trial information: ISRCTN36453794. Research Sponsor: None.

10007 Oral Abstract Session

ONITT: A phase I study of nanoliposomal irinotecan with talazoparib or temozolomide in children and young adults with recurrent or refractory solid tumors.

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Background: Talazoparib (TAL), a potent PARP inhibitor, demonstrated preclinical activity in Ewing sarcoma when combined with irinotecan (IRN) and temozolomide (TMZ). A phase I study (BMNIRN, NCT02392793) showed clinical benefit of TAL + IRN + TMZ; but dose escalation was limited due to hematologic and gastrointestinal toxicity. We therefore evaluated, for the first time in children, nanoliposomal irinotecan (nal-IRI) in combination with either TAL or TMZ. **Methods:** Patients (pts) aged 1-30 with recurrent or refractory solid tumors were eligible to receive nal-IRI + TAL (Arm A) or nal-IRI + TMZ (Arm B) using a Bayesian keyboard design. Nal-IRI dosage was escalated with fixed TAL and TMZ doses. Each cycle was 21 days. Maximum tolerated dosage(s) (MTD) and recommended phase 2 dosage(s) (RP2D) were determined. Nal-IRI and TAL plasma pharmacokinetics (PK) were evaluated. Toxicities were assessed using CTCAE v.5 and responses were evaluated by RECIST 1.1. UGT1A1 polymorphisms and serial circulating tumor DNA (ctDNA) samples were evaluated. **Results:** Forty-six pts enrolled at 5 sites. The first 9 (5 Arm A; 4 Arm B) received nal-IRI days 1, 8. Four pts had dose limiting toxicities (DLTs), so day 8 nal-IRI was removed (Amend 1). After Amend 1, 37 pts (23 male; median age 14 years, range 1-23) enrolled (19 Arm A; 18 Arm B). The most common diagnosis was Ewing sarcoma (n = 16, 35%). Table 1 summarizes DLTs in Cycle 1 and response. The most common serious adverse events included febrile neutropenia (12 Arm A; 2 Arm B), colitis (4 Arm A; 2 Arm B), vomiting (4 Arm A), and diarrhea (3 Arm A). Confirmed responses were seen in five Arm A (1 CR, 4 PR) and five Arm B (1 CR, 4 PR) pts with Ewing sarcoma, CIC-DUX4 sarcoma, synovial sarcoma, and rhabdomyosarcoma. Seven pts (5 Arm A; 2 Arm B) had stable disease. Results of PK, UGT1A1 and ctDNA will be presented. **Conclusions:** The MTDs were nal-IRI 160mg/m^2 plus TAL (Arm A) and nal-IRI 200mg/m^2 plus TMZ (Arm B). The RP2Ds are pending FDA review. These regimens are feasible with evidence of anti-tumor activity and warrant further investigation. Clinical trial information: NCT04901702. Research Sponsor: None.

Dose level	Nal-IRI mg/m^2 IV	Arm A Nal-IRI + TAL (po, 600mcg/m^2/dose) Days (D)	# of pts	Arm B Nal-IRI + TMZ (po, 100mg/m^2) Days (D)	# of pts	DLT Cycle 1 (# of pts)	Confirmed Response (CR, PR, SD, PD)
1	120	D 1: nal-IRI + TAL divided BID D 2-6: TAL daily	7	D 1: nal-IRI + TMZ D 2-5: TMZ daily	3	Arm A: 1 pt - neutropenia (1)	Arm A: CR (1), SD (1), PD (2) Arm B: PR (1), SD (1), PD (1)
2	160	D 1: nal-IRI + TAL divided BID D 2-6: TAL daily	10	D 1: nal-IRI + TMZ D 2-5: TMZ daily	3	Arm A: 3 pts - anemia (1), thrombocytopenia (1), sepsis (1), colitis (1)	Arm A: PR (3), SD (4), PD (3) Arm B: PR (1), PD (1)
3	200	D 1: nal-IRI + TAL divided BID D 2-6: TAL daily	2	D 1: nal-IRI + TMZ D 2-5: TMZ daily	12	Arm A: 2 pts – abd pain (1), thrombocytopenia (1), neutropenia (1), diarrhea (1) Arm B: 3 pts – nausea (1), neutropenia (1), sepsis (1), thrombocytopenia (1)	Arm A: PR (1) Arm B: CR (1), PR (2), SD (1), PD (6)

10008 Oral Abstract Session

Phase Ib study of the combination of regorafenib with conventional chemotherapy in patients with newly diagnosed multi-metastatic Ewing sarcoma: The Rego-Inter-Ewing-1 study.

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Background: Regorafenib monotherapy has shown interesting but limited activity against relapsed Ewing sarcoma. We present the first results of the phase Ib study to identify the maximum tolerated dose (MTD) of regorafenib in combination with standard multimodal treatment in patients with newly diagnosed multi-metastatic Ewing sarcoma (NCT05830084). **Methods:** International multi-center phase Ib study of the combination of regorafenib with interval-compressed chemotherapy (VDC/IE) in patients aged 2-50 years with newly diagnosed metastatic (excluding lung/pleura only) Ewing sarcoma. VDC/IE chemotherapy was administered at the standard doses. Regorafenib was given orally for 21 days of a 28-day cycle (from day 5) at a starting dose level of 66 mg/m^2/day (capped at 120 mg, DL0, 80% of the pediatric recommended phase 2 dose (RP2D)) and escalated to 82 mg/m^2/day (100% RPD2, capped at 160 mg, DL1) or de-escalated to 50 mg/m^2/day (60% RPD2, DL-1). The study implemented the Bayesian Optimal Interval (BOIN) design (Yuan et al, Clin Cancer Res 2016). Primary tumour local treatment was surgery and/or radiotherapy. Adjuvant therapy consisted of VC/IE cycles or high dose chemotherapy consolidation with Busulfan/Melphalan (BuMel) and autologous stem cell rescue (ASCR). Regorafenib was given concomitant to adjuvant VC/IE cycles and primary tumor radiotherapy to the extremities but permanently discontinued in those receiving BuMel/ASCR or primary tumour radiotherapy to sites other than extremities. **Results:** Thirteen patients (DL0: n=2, DL1: n= 11) with a median age of 15.2 years (range, 8.1-23.5), were enrolled between June 2023 and December 2024 in 7 centres and 3 countries. All were evaluable for toxicity. One dose-limiting toxicity (DLT) occurred in one patient at DL1 (pressure ulcer grade 2, requiring regorafenib dose interruption and reduction in a 17-year old patient). After the DLT period, one patient had regorafenib dose interruption/reduction. One patient presented with a grade 3 veno-occlusive disease after Bu-Mel/ASCR. Detailed toxicity data after the DLT period and pharmacokinetic data will be presented. At data cut-off of 21/01/2025, two patients had experienced disease progression before primary tumour local treatment, eight patients had finished all treatment cycles (three received Bu-Mel/ASCR consolidation) and three patients were on therapy. **Conclusions:** Regorafenib combined with VDC/IE chemotherapy is well tolerated with a MTD of 82 mg/m^2/day (capped 160 mg). The efficacy of the addition of regorafenib to standard multimodal treatment in newly diagnosed patients with metastatic Ewing sarcoma will be tested in the Inter-Ewing-1 trial developed by the Euro Ewing Consortium (planned initiation in Q3 2025). Recruitment to the Rego-Inter-Ewing-1 continues at DL1 (maximum 24 patients), until Inter-Ewing-1 initiates. Clinical trial information: NCT05830084. Research Sponsor: Fight Kids Cancer 2021 Call; Bayer (drug supply and partial funding for drug labelling/shipping).

10009 Oral Abstract Session

Promoting Resilience in Stress Management (PRISM): A randomized controlled trial of a psychosocial intervention for adolescents and young adults with advanced cancer.

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Background: Adolescents and Young Adults (AYAs) with advanced cancer report poor quality of life (QOL), high psychological distress, and minimal engagement in their healthcare decisions. We assessed the effect of a novel resilience coaching program with embedded elements of advance care planning (Promoting Resilience in Stress Management for Advanced Cancer, PRISM-AC) on AYA outcomes. **Methods:** We conducted a multisite randomized trial of PRISM-AC vs Usual Care (UC) among English-speaking AYAs aged 12-24 years and diagnosed with advanced cancer within 2 weeks before enrollment. PRISM-AC consists of 4 core sessions targeting AYA-endorsed "resilience resources" (skills in stress-management, goal setting, cognitive reframing and meaning-making) plus an optional session focused on elements of advance care planning (i.e., communication preferences and priorities). Participants completed surveys at baseline, 3-, 6-, 9-, and 12-months post-enrollment. The primary outcome was QOL (Pediatric Quality of Life scale) at 3-months; secondary outcomes included 3-month changes in resilience (Connor-Davidson Resilience scale) and hope (Snyder Hope scale) and trajectories of QOL, anxiety and depression (Hospital Anxiety and Depression Scale) over 12-months. We explored PRISM-AC's impact on AYA-engagement in critical healthcare conversations as documented in the electronic health record. We applied linear mixed effects regression models to examine the association between PRISM and changes in patient-reported outcomes. **Results:** We enrolled and randomized 195 AYAs (96 UC, 99 PRISM) between April/2019 and January/2024. They were mean aged 16.5 years (SD 3.9), mostly White (63%), non-Hispanic (59%), and publicly insured (53%). At 3-months, PRISM-AYAs reported significantly more improved resilience [mean change-score +1.3 (5.9) vs -1.4 (7.5), p=0.038] and hope [+2.4 (10.4) vs -2.8 (11.2), p=0.001] than UC-AYAs, although we detected no significant differences between study arms in QOL, anxiety, or depression. Over the 12-month study period, PRISM-AYAs reported progressively more improvements in QOL and anxiety, with significant differences at later time points [i.e., PRISM-associated improvements in QOL at 6 months: +3.4 (95% CI 0.1, 6.6, p=0.043) and 12 months: +6.8 (95% CI 3.3, 10.3, $p<0.001$)]. Over time, PRISM-AYAs also appeared to participate more in key healthcare discussions. **Conclusions:** A novel resilience coaching intervention led to immediately improved resilience and hope, and longer-term improvements in quality of life among AYAs with advanced cancer. Clinical trial information: NCT03668223. Research Sponsor: National Institutes of Health; National Cancer Institute; R01 CA222486.

10010 Oral Abstract Session

Longitudinal change in cardiac function after doxorubicin and dexrazoxane: A report from COG ALTE11C2.

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Background: Dexrazoxane (DRZ) has been associated with reduced adverse left ventricular (LV) remodeling shortly after doxorubicin (DOX) treatment (<5y) and preserved LV function in long-term (>15y) survivors of childhood cancer. What remains less clear are longitudinal changes in echocardiographic (echo) measures in this population. **Methods:** ALTE11C2 analyzed participants who received DOX treatment and were enrolled on COG protocols P9404, P9425, P9426, P9754, and Dana Farber Cancer Institute 95-01. Except for P9754, all other protocols featured upfront 1:1 randomization with DRZ (10:1mg/m^2 DRZ:DOX dose). Central echo remeasurements were used when possible, otherwise we used data from abstracted echo reports. Echo values were converted to age- or BSA-specific z-scores. Differences in z-scores by ±DRZ were estimated as a function of time using generalized estimating equations, adjusting for age, sex, DOX dose, chest radiotherapy, and data type (directly remeasured vs report). **Results:** 895 patients (67% male; 67% white non-Hispanic; mean age at diagnosis 11.4y; median DOX dose 360 mg/m^2; 32% chest radiotherapy) had evaluable echo data (n=2279 echos; 1581 centrally remeasured; 698 report only; mean of 1.0-1.7 echos per patient per time period, with an average of 1.4 echos per patient ≥15y). In multivariable analysis, DRZ was overall associated with more normal LV fractional shortening and less LV end-diastolic and end-systolic dilation, a pattern consistent with less subclinical dilated cardiomyopathy directionality. These cardioprotective changes associated with DRZ were seen most clearly in patients treated with DOX ≥250 mg/m^2 with this length of follow-up. **Conclusions:** DRZ exerts significant DOX cardioprotective effects on cardiac function and remodeling, detectable within 5y and persisting beyond 10y of follow-up. Research Sponsor: National Cancer Institute; P01 CA068484, R01 CA211996, U10 CA098543, U10 CA098413, U10 CA180886, U10 CA180899, U10 CA095861, UG1 CA189955; St Baldrick's Foundation, Leukemia and Lymphoma Society, Sofia's Hope, Rally Foundation.

Z-score difference by ±DRZ as a function of time, adjusted for sex, age, echo type, DOX dose, chest radiotherapy.

LV measure	Overall	Pre-treatment	<2y	2-4y	5-9y	≥10y
Fractional shortening	0.4 (0.2, 0.5) *	0.1 (-0.2, 0.5)	0.1 (-0.2, 0.5)	0.7 (0.4, 0.9) *	0.5 (0.2, 0.9) *	0.4 (0.2, 0.7) *
End-diastolic dimension	-0.2 (-0.4, -0.1) *	-0.2 (-0.4, 0.0)	-0.0 (-0.3, 0.2)	-0.4 (-0.6, -0.2) *	-0.2 (-0.5, 0.1)	-0.3 (-0.6, 0.0) *
End-systolic dimension	-0.3 (-0.5, -0.2) *	-0.2 (-0.5, 0.0)	-0.1 (-0.3, 0.1)	-0.5 (-0.7, -0.3) *	-0.4 (-0.7, -0.1) *	-0.4 (-0.7, -0.2) *
End-diastolic posterior wall thickness	0.0 (-0.1, 0.2)	-0.4 (-0.7, -0.2) *	-0.1 (-0.3, 0.2)	0.4 (0.2, 0.6) *	0.1 (-0.3, 0.5)	0.0 (-0.2, 0.3)
End-diastolic septal wall thickness	0.1 (-0.1, 0.2)	-0.2 (-0.5, 0.1)	-0.1 (-0.3, 0.2)	0.3 (0.1, 0.5) *	0.2 (-0.1, 0.5)	0.2 (-0.1, 0.4)
Thickness-to-dimension ratio (adverse remodeling=negative)	0.1 (-0.1, 0.2)	-0.3 (-0.5, 0.0)	-0.1 (-0.3, 0.2)	0.4 (0.2, 0.7) *	0.1 (-0.3, 0.6)	0.1 (-0.2, 0.4)
Mass	-0.1 (-0.2, 0.1)	-0.4 (-0.6, -0.1) *	-0.0 (-0.3, 0.2)	0.1 (-0.2, 0.3)	-0.3 (-0.9, 0.3)	0.2 (-0.1, 0.6)

*$p<0.05$.

10011 Oral Abstract Session

Long-term off-label MAPK inhibitor therapy in children with severe/refractory Langerhans cell histiocytosis: An international observational study of 277 cases.

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Background: Long-term off-label use of MAP kinase inhibitors (MAPKi) to treat, refractory childhood Langerhans cell histiocytosis (LCH) was evaluated within the European consortium for histiocytosis network (www.echo-histio.net). **Methods:** 277 patients from 26 countries treated with MAPKi were classified according to the clinical indication: refractory risk organ positive/negative (RO+/RO-), isolated lung destruction (Lung), sclerosing cholangitis (SC), neurodegeneration (ND), and diabetes insipidus (DI). 252 patients had received one or several lines of chemotherapies prior to MAPKi: VBL/steroids (n = 243) then 2CdA/AraC (n = 48), 2CdA alone (n = 52), clofarabine (n = 5), VCR/AraC (n = 70) before being considered refractory. The 25 treated front line by MAPKi were newborn with aggressive disease (n = 7), or had chronic manifestations like ND, SC or DI. *BRAFV600E* was detected in 95% of the cases. **Results:** Median age at diagnosis was 1.3 years. MAPKi indication was RO+ (n = 138); RO− (n = 72); Lung (n = 7); SC (n = 9), ND (n = 45), DI (n = 2). Median age at MAPKi onset was 2.3 years, with median follow-up of 3.5 years (IQR 1.6-5.9). Vemurafenib (n = 177), Dabrafenib (n = 105), Encorafenib (n = 3), Cobimetinib (n = 41), Tramatinib (n = 41), and Binimetinib (n = 1) were prescribed mainly in monotherapy, sometimes (n = 44) with various chemotherapies or HSCT (n = 5). The short-term response (before wk 8) varied from 98% in RO+ and RO-, to 30% in Lung to a null response in ND, DI and SC, although some long-term response (after 6 months) was observed in Lung and ND. Skin rash was the most frequent adverse event (AE), affecting 55% of patients. Other AEs were observed in 7 (cardiomyopathy n = 1, retinitis n = 6). Five tumors or malignancies were observed not related to MAPKi; only in patients heavily treated by 2CdA, AraC or Clofarabine. Six deaths were observed; 5-year survival was 98%. MAPKi discontinuation for 111 patients led to LCH 66 reactivations. None of the various empirical maintenance therapies used was able to prevent secondary reactivation. Among the 133 assessable patients free of ND at MAPKi initiation, ND was observed in 52 with a 5-year risk of 55%. In some cases, ND was reversible after MAPKi dose adaptation. **Conclusions:** MAPKi appeared quick, safe and effective in children with refractory LCH while the response to Lung, SC, DI and ND was limited or delayed. Further studies are needed to find effective maintenance therapy. ND should be monitored in the follow up of patients treated by MAPKi. Research Sponsor: Association Histiocytose france.

10012 Oral Abstract Session

Understanding the molecular landscape of rare tumors through the CCDI-COG Molecular Characterization Initiative.

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Background: Through collaboration with the National Cancer Institute as part of the Childhood Cancer Data Initiative, the Children's Oncology Group offers prompt paired tissue and germline sequencing for newly diagnosed rare tumor subtypes. **Methods:** Individuals are eligible for paired germline and somatic blood/tissue sequencing if they are age 25 or younger, have been diagnosed with a rare tumor in the past 6 months and have both germline and tissue samples available. The paired samples undergo DNA and RNA extraction, followed by whole exome sequencing (paired tumor and germline) of cancer associated genes and RNA targeted fusion analysis. Results are returned to the primary institution within 2-3 weeks of receipt of both samples. **Results:** Between 09/12/2022 and 11/01/2024, 490 individuals from 123 institutions were enrolled with a total of 98 distinct diagnoses reported. The most common diagnosis groups were thyroid carcinoma (n = 120), neuroendocrine tumors (n = 53), sex cord stromal tumors (n = 41), and other carcinomas (n = 83). Of the 490 patients enrolled, 438 had submitted samples with successful return of exome results in 351/438 (80.1%) and fusion results in 302/438 (69.1%) by the data cut. Tier I/II germline single nucleotide (SNV) or copy number (CNV) variants were identified in 88 (25.1%) of patients that completed sequencing. The most prevalent germline alterations included SNVs in DICER1 (n = 20, 5.7%), TP53 (n = 7, 2.0%), RB1 (n = 7, 2.0%), CHEK2 (n = 6, 17%), SDHB (n = 5, 1.4%) and VHL (n = 5, 1.4%). 98% of samples demonstrated a Tier I/II somatic variant across 26 genes, most commonly found in DICER1 (n = 39, 11.1%), BRAF (n = 30, 8.5%), TP53 (n = 22, 6.3%) and CTNNB1 (n = 14, 4.0%). RNA fusion analysis identified positive results in 22.8% of samples. Testing identified over 33 distinct fusions. Fusions were most commonly associated with thyroid cancer; RET in 16 and NTRK in 12, or desmoplastic small round cell tumor; EWSR1::WT1 in 8. In 16.5% (n = 58) of the samples, the final diagnosis was refined based on the results of the molecular testing and 6.8% (n = 24) of the centers reported using a commercially available treatment targeting an identified molecular alternation. **Conclusions:** The MCI has enabled access to genetic sequencing to patients across the Children's Oncology Group across a wide range of rare tumor diagnoses. Information about the available data can be accessed through the CCDI Hub Explore. Germline cancer predisposition was identified in a quarter of these samples, highlighting the importance of tumor-normal profiling to allow genetic counselling in these patients and appropriate surveillance. These results have the potential for lasting impact on understanding and treating individuals with rare cancers and the development of targeted future clinical trials. Research Sponsor: National Cancer Institute.

10013 Oral Abstract Session

CCDI-COG molecular characterization initiative: The expanding data on childhood cancer.

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Background: The Molecular Characterization Initiative (MCI), a collaboration between the Children's Oncology Group (COG) and the NCIs Childhood Cancer Data Initiative (CCDI) which is intended to define a standardized genomic characterization of pediatric cancer, provides rapid, clinical sequencing for newly diagnosed central nervous system (CNS) tumors, rare tumors, soft tissue sarcomas (STS), or advanced stage neuroblastoma (NB) to guide diagnosis and treatment for these children. **Methods:** Patients enrolled on APEC14B1-MCI who are ≤25 years of age with an eligible tumor type treated at national or international COG sites with available snap frozen or FFPE tissue and paired germline samples undergo RNA/DNA extraction. Whole exome sequencing (paired tumor and germline), targeted RNA fusion (excluding NB) and methylation array (CNS clinical / STS, NB and rare tumor research only) analyses are performed, with clinical results returned in 2-3 weeks. **Results:** Between 3/31/22 and 11/1/24, MCI provided results for 3,972 patients, including 2,666 with CNS tumors, 781 with STS, 372 with rare tumors and 153 with NB, across 188 institutions. 89% of the > 10,000 individual tests resulted within 2 weeks of receiving nucleic acids for sequencing. Tier I/II germline single nucleotide (SNV) or copy number (CNV) variants were identified in 528 (14.1%) patients [10.4% (NB) to 25.1% (rare tumors)]. The most common germline alterations included SNVs in *TP53* (n = 52,1.4%), *CHEK2* (n = 50,1.3%), *DICER1* (n = 35,0.93%), *NF1* (n = 29,0.78%) and *ATM* (n = 24, 0.64%). Somatic SNVs or CNVs were identified in 85% of samples overall. Somatic SNVs most commonly involved TP53 (n = 309,8.3%), BRAF (n = 222,6.9%), or CTNNB1 (n = 166,4.4%). Targeted RNA sequencing identified gene fusions in 30% overall (23% rare, 27% CNS, 40% STS). Methylation array resulted in positive subclassification of CNS tumors in 90% of patients, including 522 patients with medulloblastoma. Additional characterization of residual nucleic acid samples is planned, with data available through the database of Genotypes and Phenotypes (dbGaP). Follow up data has been collected for 1236 patients (NCI-CCDI Hub), including frontline treatment (chemotherapy and/or radiation), response to therapy, and vital status. Additionally, 749 reported on the utility of MCI testing six months following enrollment. MCI results were used for: enrollment on a clinical trial (n = 86,11.5%), treatment with a targeted therapy (n = 8,10.7%), and/or refining the pathologic diagnosis (n = 223,29.5%). **Conclusions:** The MCI has resulted > 10,000 sequencing assays from 3,972 children with cancer in 31 months. This has directly impacted the diagnosis and/or management of patients with newly diagnosed tumors, providing access to timely molecular testing (including methylation in CNS tumors and fusion testing in STS), and guiding therapy and clinical trial enrollment for many patients. Research Sponsor: None.

10014 Oral Abstract Session

Genomic newborn screening for cancer risk: A retrospective cohort study.

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Background: Population-based newborn screening (NBS) improves outcomes through early detection of rare pediatric conditions. Cancer is a leading cause of pediatric morbidity and mortality, but biomarkers for cancer risk are not included in NBS. NBS for detection of germline variants in genes associated with elevated risks of early onset childhood cancer could promote surveillance and early detection. **Methods:** Infants born in Michigan between 1987 and 2020 who developed a solid or CNS tumor before age 8 were identified through the Michigan Cancer Registry and linked to the state dried blood spot (DBS) biobank. DNA was extracted from 3.2 mm DBS punches and underwent t-NGS of 11 early-onset cancer predisposition genes (*RB1, TP53, WT1, RET, SMARCB1, PTCH1, SUFU, APC, DICER1, ALK* and *PHOX2b)*. Deleterious single nucleotide, short insertion and deletion variants (SNV/indels) and copy number variants (CNVs) were identified using an automated variant classification platform (Fabric Genomics) including Clinvar classification. CNV's were manually reviewed for evidence of deletion of at least one exon in a targeted gene. **Results:** 1948 DBS from infants who developed a solid or brain cancer before age 8 were identified. DNA extraction and tNGS with $>$ 20X coverage was successful for 99.9% of DBS. A heterozygous deleterious variant was detected in 133 infants (116 SNV/indels and 17 CNVs), or 6.8% of the cohort. The distribution, by diagnostic group and gene is shown below. No activating ALK variants were detected. Germline deleterious predisposition variants (PV) in *RB1* were detected in 40/50 bilateral retinoblastoma cases. 14/132 (11%) of medulloblastoma cases demonstrated a PV involving *SUFU* (6), *PTCH1* (3), *SMARCB1* (4) or *TP53* (1). Heterozygous PV in *RET* were detected in 6/6 medullary thyroid carcinoma cases. Median age at cancer diagnosis was 14 months in cases with PV compared to 32 months in cases without PV ($p < .001$). Lower overall survival was noted in sarcoma cases with PV vs. those without PV and in brain tumor cases with PV vs. those without (Logrank test, $p = .04$ and $p < .004$, respectively). PV carriers developed proportionally more second cancers (9.5% vs 5%; $p = 0.02$) and 20% of PV carriers who received radiation therapy developed second cancers. **Conclusions:** Population-based genomic NBS could identify newborns at risk for early onset childhood cancers, enabling early surveillance, diagnosis and treatment. Inclusion of *RB1* in a NBS test would identify 80% of children at risk for bilateral retinoblastoma. Further research focused on implementation of NBS for cancer risk is needed. Research Sponsor: Bridge Foundation.

Diagnosis Group	Overall N=1948	No (%) with a variant	*Count of deleterious variants (combined CNV and SNV/indel) for each gene*									
			RB1	*TP53*	*WT1*	*PTCH1*	*SUFU*	*DICER1*	*SMARCB1*	*RET*	*PHOX2b*	*APC*
CNS tumors	667	28 (4%)	1	9		3	6	1	7		1	
Renal Tumors	309	10 (3%)		1	7			1	1			
Sarcoma	193	13 (7%)		10		1		2				
Retinoblastoma	167	67 (40%)	67									
Liver Tumors	87	3 (3%)		1								2
Neuroblastoma	450	1 (<1%)										1
Rare/Other	75	11 (15%)	1	3				1		6		

10015 Oral Abstract Session

The gut microbiome in pediatric diffuse midline gliomas: Correlative study results from the PNOC022 trial.

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Background: The gut microbiome exerts a multifaceted influence on treatment outcomes across various cancers, yet its potential role in diffuse midline gliomas (DMGs) remains under-explored. In this report, we present the gut microbiome findings from cohort 2 in the DMG–Adaptive Combination Trial (DMG-ACT, PNOC022). **Methods:** PNOC022 is an open-label, multi-institutional, international clinical trial using a Bayesian drug combination platform trial design. This report focuses on the combination therapy arm involving dordaviprone and paxalisib, administered to patients (aged 2–39 years) who had completed standard-of-care radiation therapy (Cohort 2). Stool samples were collected at baseline (n = 22), cycle 1 day 1 (n = 15), cycle 7 day 1 (n = 9), and at progression (n = 4). Microbiome profiling was performed with shotgun metagenomic sequencing (NovaSeq X Plus Series, PE150). Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method. Longitudinal shifts in microbial communities were evaluated using α-diversity (Shannon-index) and β-diversity (Bray-Curtis dissimilarity index). Baseline α-diversity associations with PFS and OS were examined with log-rank tests and further validated through age-adjusted Cox regression analysis. **Results:** Between November 2021 and October 2023, 69 biopsy-confirmed DMG patients enrolled (median age 9 years [range 3-37], n = 42 female [61%]) in cohort 2. Median OS from time of diagnosis was 15.6 months (95% CI 12.9-19.5), with a median follow-up time of 19.5 months (95% CI 17.9-23.9). Microbiome analyses were performed for 33 DMG patients (48%). Alpha-diversity and β-diversity remained stable across timepoints. Using baseline samples (n = 22) and a median α-diversity cutoff of the respective group's values, patients were stratified into two categories (low- vs. high-diversity). Low-diversity was associated with significantly worse PFS and trended worse for OS, resulting in a 6-month PFS: 73% (95%CI 51-100) vs. 100%; $p < 0.001$) and 12-month OS: 46% (95%CI 24-87) vs. 78% (95%CI 55-100; p = 0.19). Validation using age adjusted Cox regression analysis confirmed a decrease in the risk of progression or death with increasing α-diversity. PFS hazard ratio (HR) was 0.2 (95% CI: 0.1–0.5; $p < 0.01$) and OS HR was 0.3 (95% CI: 0.1–0.7; $p < 0.01$). **Conclusions:** Baseline high alpha-diversity in the gut microbiome is significantly associated with improved PFS and trended towards improved OS in pediatric patients with DMG in cohort 2 of PNOC022. Age-adjusted survival models reinforced its prognostic value for PFS and OS. These findings highlight the potential impact the gut microbiome has on outcomes and will be explored further and warrant our ongoing investigation in PNOC022. Research Sponsor: PNOC FOUNDATION; ChadTough Defeat DIPG; DDRFA; Storm the Heavens; Musella Foundation.

10016 Oral Abstract Session

Cognitive outcomes following proton vs. photon radiotherapy for CNS non-germinomatous germ cell tumors: A Children's Oncology Group study.

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Background: The Children's Oncology Group (COG) study ACNS1123 (stratum 1) treated children with localized non-germinomatous germ cell tumors (NGGCT) of the brain with chemotherapy followed by whole ventricular (WV) radiotherapy (RT, 30.6 Gy) followed by a focal tumor bed boost (54 Gy total dose). Previous work has shown that WVRT with proton therapy, compared to photon RT, resulted in lower RT doses to the brain. However, it was unclear whether this dosimetric difference led to superior cognitive outcomes. **Methods:** The ACNS1123 study was a prospective, phase II trial conducted by the COG that enrolled 107 patients. Evaluation of cognitive functioning of children was a co-primary objective of the study. Cognition was prospectively examined at 9, 30 and 60 months post-diagnosis, using the COG Standard Neuropsychological and Behavioral Battery. The primary endpoints were attention/concentration, estimated intelligence quotient (IQ), and processing speed. Linear mixed-effect models were created to model cognitive endpoints with treatment exposures, including RT modality (proton vs. photon RT) or RT dose to brain structures. Cognitive evaluations completed post-recurrence were excluded. **Results:** Seventy patients were evaluable and received WVRT followed by RT boost, of which 20 received proton therapy. Mean age of all patients was 11.8 $\pm$ 4.3 years old at the start WVRT, and were predominantly male (n = 52). Mean doses to the brain were significantly lower with proton vs. photon RT (mean 18.8 $\pm$ 1.8 [SD] vs. 24.7 $\pm$ 3.7 Gy, $p < 0.0001$), left hippocampus (41.1 $\pm$ 5.2 vs 46.2 $\pm$ 5.3 Gy, $p = 0.0005$), and right hippocampus (41.8 $\pm$ 5.1 vs 46.0 $\pm$ 5.3Gy, $p = 0.0038$). A total of 56, 60 and 61 patients were evaluable for attention/concentration, estimated IQ and processing speed, respectively, with 1 or more evaluation. Nine, 20 and 20 patients had data at all 3 time points for attention/concentration, estimated IQ and processing speed, respectively. Multivariable modelling demonstrated that photon therapy was associated with a decline in IQ over time ($p = 0.0401$), as compared with proton RT, adjusted for age at RT and gender. In a separate multivariable model, higher mean brain dose was also associated with poorer recovery of IQ over time ($p = 0.0216$), adjusted for gender. There were no identified associations between use of proton RT or hippocampal dose with processing speed or attention/concentration. **Conclusions:** Compared to proton therapy,WVRT delivered with photons was associated with a significant decline in IQ and adverse recovery of IQ over time. To our knowledge, this data is the first to demonstrate such an association for children with NGGCT. Research Sponsor: None.

10017 Oral Abstract Session

Efficacy and safety of dordaviprone (ONC201) in prospective clinical trials of adult and pediatric recurrent H3 K27M-mutant diffuse glioma patients.

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Background: Dordaviprone (ONC201), a first in class imipridone, has demonstrated safety and efficacy in an integrated analysis of patients with recurrent H3 K27M-mutant diffuse midline glioma across clinical studies. Here, we report efficacy and safety findings from two prospectively defined clinical trial arms that evaluated single-agent dordaviprone response in recurrent H3 K27M-mutant glioma. **Methods:** Phase 2 trialONC013 (Arm B) and Phase 1 trial ONC014 (Arm F) were designed to evaluate the objective response rate (ORR) by RANO-HGG criteria of dordaviprone in adult and pediatric patients, respectively, with recurrent H3 K27M-mutant diffuse glioma. Open label dordaviprone was administered once weekly at 625 mg for adults and at a dose scaled by body weight for pediatrics. Responses were investigator-assessed by RANO criteria. Eligibility required measurable enhancing recurrence by RANO-HGG criteria, radiotherapy completed ≥90 days prior to dordaviprone unless unequivocal progression qualified per RANO, Karnofsky or Lansky performance status >60. DIPG, spinal tumors, leptomeningeal disease, and CSF dissemination were excluded. **Results:** ONC013 Arm B enrolled 30 patients (median age 32, range, 21-66 years) with the majority having a primary midline non-brainstem tumor (n = 19, 63.3%) and one prior recurrence (n = 22, 73.3%). The ORR was 16.7% (95% CI, 5.6-34.7) with 5 partial responses (PR). The median duration of response (DOR) and time to response (TTR) were 15.1 months (7.5-not reached) and 3.8 months (1.8-4.6), respectively. Three patients experienced a grade ≥3 treatment-related adverse events (TR-AE), none had treatment-related serious AEs (TR-SAEs), and 1 had TR-AE leading to dose reduction (ALT increase). ONC014 Arm F enrolled 11 patients (median age 14, range 11-19 years). Most had a primary midline non-brainstem tumor (n = 7, 63.6%) and 1 prior recurrence (n = 6, 65.6%). Two (18.2%) radiographic responses were reported, 1 response (9.1%) qualified by RANO criteria. One PR occurred with > 95% tumor regression and an 8.5-month DOR (1.9-month TTR). Another patient experienced a > 50% tumor regression (4.3-month TTR) that did not meet RANO PR criteria due to initiation of 2.5 mg dexamethasone post-baseline. 12-month PFS rate was not reached; 12-month OS rate was 27.3% (6.5, 53.9). One patient experienced a grade ≥3 TR-TEAE (9.1%); no TR-SAEs, treatment-related deaths, or TR-AE leading to treatment discontinuation occurred. **Conclusions:** In prospective clinical trials designed to evaluate ORR, single-agent dordaviprone response and safety in adult and pediatric recurrent H3 K27M-mutant diffuse glioma were similar to previously pooled analyses. Clinical trial information: NCT03295396 and NCT03416530. Research Sponsor: Chimerix, Inc.

10018 Rapid Oral Abstract Session

Metabolic-only response assessment for omission of residual node radiation therapy (RNRT) for patients with classical Hodgkin lymphoma (cHL) and impact on event free (EFS) and overall survival (OS): A report from the Pediatric Hodgkin Consortium's phase 2 study cHOD17 (NCT03755804).

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Background: The AEPA/CAPDac (brentuximab vedotin, etoposide, prednisone, doxorubicin [cumulative dose = 160mg/m^2], cyclophosphamide, vincristine, prednisone, and dacarbazine) regimen results in excellent EFS and OS rates for pediatric cHL but resulted in 65% of patients requiring RNRT using metabolic and anatomic response criteria. We aimed to determine if use of a metabolic-only response assessment would allow omission of consolidative prednisone and RNRT for the majority of high-risk patients while maintaining a high EFS. **Methods:** cHOD17 is an open-label, single-arm, multicenter, phase 2 trial with a stratum for patients ≤25 yrs of age at diagnosis of high-risk (stage IIB, IIIB, or IV), CD30+ cHL. ^{18}FDG-PET only (rather than + anatomic) was used to guide therapy following 2 cycles of AEPA [adapted from the HLHR13 trial (NCT01920932), without mandated growth factor] at the early response assessment (ERA). Complete (CMR) and inadequate metabolic responses (IR) were defined as Deauville ≤3 and ≥4, respectively. Patients in overall CMR received 4 CADac cycles without prednisone or RNRT. IR patients received 4 CAPDac (with prednisone) followed by consolidative IR site directed RNRT (25.5 Gy). The primary objective was to estimate EFS utilizing this approach. **Results:** 114 patients were enrolled at 7 institutions from January 2019 to February 2024. Median (range) age at diagnosis was 16.4 (6.7-24.1) yrs and follow-up 2.5 (0.4-5.7) yrs. Most (79.8%) were nodular sclerosing histology. Stages included 22.8% IIB, 16.7% IIIB, 20.2% IVA, and 40.4% IVB. One patient discontinued therapy due to treatment-related toxicity and was unavailable for response assessment. Of 113 remaining, 69 (61.1%) achieved a CMR at ERA and were spared RNRT and glucocorticoids during the CAPDac cycles. The 2-yr EFS was 94.7% (95% CI: 90.3%-99.4%) and OS 100% (95% CI: 100%-100%). Five of six relapses (< 3 mo (N = 1), 3-12 mo (N = 2), and > 12 mos (N = 3) following therapy) occurred in individuals with an IR. The most frequent grade ≥3 toxicities were lymphopenia (84.2%) and neutropenia (91.2%). Grade 3 and 4 febrile neutropenia occurred in 21.1% and 1%, respectively. Neuropathy grade ≥3 was not observed. Serious adverse events were rare (n = 4) and included: multi-organ failure during cycle 1 that recovered (n = 2), therapy-related myeloid leukemia in remission following allotransplant (n = 1), and infection-related death during allotransplant for relapse (n = 1). **Conclusions:** A metabolic-only response assessment in the AEPA-CAPDac regimen results in high rates of omission of consolidative RT and glucocorticoids while limiting cumulative anthracycline exposure and maintaining excellent 2-year EFS of 94.7% and OS of 100%. Clinical trial information: NCT03755804. Research Sponsor: Supported by Seagen Inc, which was acquired by Pfizer in December 2023.

10019 Rapid Oral Abstract Session

Second malignant neoplasm risk after mediastinal radiotherapy for pediatric Hodgkin lymphoma on Children's Oncology Group AHOD1331.

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Background: The reported incidence of second malignant neoplasms (SMN) in long-term survivors of Hodgkin lymphoma (HL) is derived from patients treated with outdated radiation therapy (RT) techniques. We modeled the risk of SMN in pediatric patients with high-risk classic HL treated with modern mediastinal RT. **Methods:** In patients who received mediastinal RT on the Children's Oncology Group study AHOD1331, we modeled the lifetime attributable risk (LAR) at 70 years of age of thyroid, lung, and breast carcinoma. This value indicates the absolute increased risk of SMN at 70 years of age due to RT, above the baseline population risk (mean baseline rates at 70 years of age are 0.7%, 3.3%, and 8.9% for thyroid, lung, and breast carcinoma, respectively, https://seer.cancer.gov/data/). **Results:** In 296 patients who received protocol-directed mediastinal RT, median age at diagnosis was 15.1 years, 55% were female, and 98% had large mediastinal adenopathy. Following 5 cycles of chemotherapy, patients received RT targeting the mediastinum based on criteria of this study; in addition, some patients received RT to other supradiaphragmatic sites that contained slowly responding lesions, including the axilla (n = 3, 1%), lung (n = 7, 2.4%), upper neck (n = 4, 1.3%), and lower neck (n = 8, 2.7%). The RT modality was proton therapy in 25.3%, photon intensity modulated RT (IMRT) in 45.6%, and photon 3-dimensional conformal RT (3D-CRT) in 27.7%. The RT prescription dose was 21 Gy in 83% and 30 Gy in 16% who had a partial metabolic response at the completion of chemotherapy. The mean (range) doses to the thyroid, lungs, and breasts were 12.8 Gy (0–30.3), 8.0 Gy (0.1–15.2), and 4.2 Gy (0.2–14.5), respectively. For the complete cohort, the mean LAR at 70 years of age of thyroid carcinoma was 0.063% and of lung carcinoma was 5.34%. For females, the mean LAR at 70 years of age of breast carcinoma was 2.92%. The Table summarizes the LAR for each SMN, stratified by RT modality. **Conclusions:** In patients treated with mediastinal RT on a recent multi-institutional study of pediatric HL, the predicted long-term risk of SMN is substantially lower than in historical cohorts. Clinicians should consider the toxicity associated with a current RT approach when selecting therapies and counseling patients. Clinical trial information: NCT02166463, this is a post hoc modeling study that includes patients enrolled on this study. Research Sponsor: None.

Mean [range] lifetime attributable risk (%) at an attained age of 70 years for thyroid, lung, and breast carcinoma.

	Thyroid	Lung	Breast (females)
3D-CRT	0.046 [0.002-0.332] N=81	5.07 [0.12-10.82] N=82	1.82 [0.67-5.98] N=46
IMRT	0.064 [0.001-0.386] N=135	6.24 [2.22-11.79] N=135	4.36 [0.66-8.43] N=76
Proton	0.086 [0-1.160] N=74	4.15 [0.94-7.77] N=75	1.45 [0.17-7.23] N=40

10020 Rapid Oral Abstract Session

Mortality in survivors of childhood cancer diagnosed with subsequent thyroid cancer: A report from the Childhood Cancer Survivor Study.

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Background: Childhood cancer survivors are at increased risk of developing a subsequent thyroid cancer, particularly following radiotherapy. In the general population, thyroid cancer has a very low mortality rate. Mortality after a diagnosis of subsequent thyroid cancer in survivors is unknown. **Methods:** We calculated the standardized mortality ratio (SMR) following the development of subsequent thyroid cancer in a cohort of 24,683 5-year survivors of childhood cancer diagnosed between 1970 and 1999 using the age-sex-calendar-year-specific general population all-cause mortality rates from the CDC as the reference rates. We estimated all-cause mortality post the diagnosis of thyroid cancer (time-dependent covariate), adjusting for development of other subsequent malignant neoplasms (SMN) and chronic health conditions (CHC), using a piecewise exponential model. Thyroid cancer-specific mortality among survivors was compared to SEER cases with thyroid cancer, adjusting for age, sex, race and calendar-year. SEER data was also used to compare thyroid cancer characteristics in childhood cancer survivors with thyroid cancer patients without a history of childhood cancer. **Results:** Among 397 survivors with subsequent thyroid cancer, 63% were female, 83% had received radiotherapy for treatment of their primary childhood cancer with fields that included the thyroid gland, and 92% had at least one severe or life-threatening chronic condition. Thyroid tumor size was significantly smaller in survivors, with 33% of cases in survivors and 24% in SEER being less than 1 cm ($p < 0.001$). There were 82 deaths with 7 deaths due to thyroid cancer. Within the cohort of survivors of childhood cancer, the rate of all-cause mortality did not increase with a diagnosis of thyroid cancer, adjusting for development of other SMNs and CHCs (RR = 1.0, p = 0.96), but it was 7 times higher than that of the general population (SMR = 6.9, 95% CI 5.5-8.5). Compared to adults diagnosed with thyroid cancer in the general population, survivors with subsequent thyroid cancer did not have an increased risk of thyroid cancer-specific death (RR = 0.9, 95% CI 0.4-1.9). Mortality risk was higher among those with older age at subsequent thyroid cancer diagnosis, male sex, Black and Hispanic race and ethnicity and tumor size $>$ 1 cm. **Conclusions:** The rate of all-cause mortality does not increase with a diagnosis of subsequent thyroid cancer in childhood cancer survivors. This finding suggests that thyroid cancer screening in this population should be based on reducing morbidity since it likely will not provide survival benefit. Enhanced attention to CHC management may be critical for long-term survival. Research Sponsor: U.S. National Institutes of Health.

10021 Rapid Oral Abstract Session

Social determinants of health (SDOH) and late mortality among survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS).

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Background: Neighborhood-level SDOH may increase disparities in adverse cancer-related outcomes. The US CDC-constructed Social Vulnerability Index (SVI) reflects 4 SDOH domains (socioeconomic status [SES]; household composition; minority status/language; housing/transportation) and captures the vulnerability of underserved communities. The impact of neighborhood-level SDOH on late mortality among survivors of childhood cancer is not known. **Methods:** Analyses included 5-year survivors in the US diagnosed in 1970-1999 participating in the CCSS, a multi-institutional retrospective cohort study. We evaluated geocoded SVI quintiles (Q1 to Q5, from least to most vulnerable) based on residential addresses and personal SES factors including income, education level, and health insurance status collected at CCSS baseline. The impact of SVI and personal-level SES on all-cause and cause-specific mortality rates were evaluated using cumulative incidence and relative rates (RRs) from piecewise exponential regression models adjusted for age, sex, diagnosis age, and treatments. **Results:** Among 20,261 survivors with geocode data (mean age at cancer diagnosis and baseline evaluation, 7y and 24y respectively, with a mean follow up of 17y), 2,439 survivors died. All-cause late mortality was greater in survivors living in more vulnerable areas (Q5 vs. Q1, at 20y: 14.7% vs. 10.8%, $P<0.001$). We observed a dose-response relationship between worsening SVI and the all-cause mortality rate (Q5 vs. Q1 RR 1.52, 95% CI 1.32-1.76, $P_{trend}<0.001$) as well as for mortality rates due to specific health causes (Table). Among the SDOH domains, neighborhood SES (Q5 vs. Q1 RR 1.68, 95% CI 1.45-1.95) showed the strongest association with all-cause mortality followed by household composition (RR 1.43, 95% CI 1.24-1.66). Notably, these findings remained largely consistent after adjusting for personal-level SES as well as in analyses stratified by income and insurance coverage. **Conclusions:** Living in socially vulnerable neighborhoods during young adulthood is associated with a ~50% increased risk for late mortality among survivors of childhood cancer and is largely unaffected by favorable personal-level SES. Policies and interventions targeting neighborhood-level SDOH during the transition to survivorship care are needed to reduce mortality risk in this population. Research Sponsor: None.

Adjusted RRs and 95% confidence intervals for overall and cause-specific mortality.

SVI	All cause	Subsequent neoplasm cause	Cardiovascular cause	Other health causes
Q2	1.00 (0.88 - 1.14)	0.90 (0.74 - 1.11)	1.09 (0.76 - 1.55)	1.09 (0.85 - 1.39)
Q3	1.16 (1.02 - 1.32)	1.03 (0.84 - 1.27)	1.18 (0.82 - 1.70)	1.24 (0.97 - 1.59)
Q4	1.24 (1.08 - 1.42)	1.12 (0.90 - 1.39)	1.29 (0.88 - 1.90)	1.44 (1.11 - 1.86)
Q5	1.52 (1.32 - 1.76)	1.35 (1.07 - 1.69)	1.54 (1.02 - 2.33)	1.83 (1.38 - 2.42)

SVI Q1 (least vulnerable) is the referent.

10022 Rapid Oral Abstract Session

Five-year cardiomyopathy risk prediction in survivors of childhood cancer using electrocardiogram.

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Background: Childhood cancer survivors (CCS) face an increased risk of developing cardiomyopathy during adult life due to late onset of treatment (e.g. anthracyclines and chest directed radiation) associated cardiotoxicity. Early identification of survivors at elevated risk using low cost and easily accessible data modalities can identify survivors in need of echocardiographic screening. Our goal is to utilize 12-lead electrocardiogram (ECG) develop and externally validate an artificial intelligence model (ECG-AI) for prediction of five-year risk for cardiomyopathy among CCS. **Methods:** We developed three deep learning models including a modified ResNet (a convolutional neural network architecture), an encoder-attention network, and a dual attention network to predict cardiomyopathy risk from 10 second 12-lead ECGs. We used the St Jude Lifetime Cohort Study (SJLIFE) for model building using a 60/20/20 patient-level split for training, validation, and holdout testing. We evaluated model performance for all cardiomyopathy grades (Common Terminology Criteria for Adverse Events) and specifically grade 3 (severe) cases. The final model was externally validated in the Dutch Childhood Cancer Survivor Study (DCCSS-LATER) cohort. For the DCCSS-LATER cohort, we evaluated accuracy of ECG-AI for the five-year cardiomyopathy risk prediction. **Results:** SJLIFE analytical cohort included 7,632 ECGs from 4,795 unique participants with no cardiomyopathy. 228 participants developed cardiomyopathy at least one year after index ECG date. Participants were 79% white, 11% Black, and 49% male with mean age at ECG of 33±10 years. In SJLIFE holdout, the encoder-attention model achieved the highest performance (area under the receiver operating characteristic curve (AUC) 0.75 for all grades and 0.84 for ≥grade 3 cases). The modified ResNet and dual attention models achieved AUCs of 0.69 and 0.72, respectively. DCCSS-LATER data included 749 ECGs with from 330 unique patients (48% male, age at ECG of 28±10 years). 22 patients developed cardiomyopathy at least one year after index ECG date. The encoder-attention model achieved an AUC of 0.74 for 5-year cardiomyopathy risk prediction. We note that the cardiomyopathy grading was not available in DCCSS-LATER, this study instead used a broader cardiomyopathy diagnosis information. **Conclusions:** ECG-AI analysis of standard 10 second 12-lead ECGs can identify childhood cancer survivors at risk for future cardiomyopathy with moderate to high accuracy depending on the cardiomyopathy severity. Future studies will focus on improving accuracy by incorporating clinical data such as B-type natriuretic peptides, left ventricular ejection fraction. Research Sponsor: National Cancer Institute; R01CA261834.

10023 Rapid Oral Abstract Session

Does early phase study enrollment for pediatric oncology patients have an impact on symptom burden and quality of life (QOL)? A national Canadian study report.

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Background: There are few therapeutic options for pediatric patients with relapsed or refractory cancers. The impact of early phase trial enrolment on the quality of life (QOL) and symptom burden in this patient population is unknown. We hypothesized that this information could inform future clinical trial design and would be of value to clinicians, patients and their families. The primary aim was to determine if those enrolled on a phase I or II trial had improved QOL measured using the PedsQL 3.0 Acute cancer Module compared to those eligible, not not enrolled on a trial. **Methods:** In this Canadian multi-site study, we included patients 2-18 years of age who were enrolled on a phase I/II clinical trial and those who would have been eligible but did not enroll. The PedsQL 3.0 Acute Cancer Module was completed at baseline, week 4 and week 8 by guardians and by patients, for those age 5 and older. The PedsQL 3.0 Acute Cancer Module total scores were compared separately for patients and guardians using a mixed linear registration model with a random effect for a patient. **Results:** Of the 80 patients, 31 (39%) patients were enrolled on an early phase trial and 49 (61%) were not enrolled. The majority of patients had a brain tumor (63.3% of those enrolled; 32.7% of those not), followed by a bone tumor (16.7% of those enrolled; 24.5% of those not). In both groups, the majority of patient were included at the time of their first relapse (64.5% of those enrolled and 69.9% of those not). No significant difference was found between PedsQL3.0 patients or guardians; $p = 0.09$). The PedsQL3.0 total scores were significantly higher for patients enrolled on an early phase trial compared to those patients not enrolled ($p = 0.01$). However, after adjusting for baseline levels, the difference between enrolled patients vs not was not statistically significant ($p = 0.8$). **Conclusions:** Being enrolled on an early phase trial does not appear to have a negative effect on one's quality of life. The results have also demonstrated that it is feasible to evaluate patients enrolled and not enrolled on early phase trials and compare their symptom experience using the PedsQL 3.0 Acute cancer Module. Continued efforts will focus on more recruitment and using SSPedi to further investigate differences in QOL. This research is supported through C17 Council, Kindred Foundation and the CHEO Research Institute. Research Sponsor: C17; Kindred Foundation; The Children's Hospital of Eastern Ontario Research Institute.

10024 Rapid Oral Abstract Session

Determining the recommended phase 2 dose (RP2D) of dose-intense irinotecan combined with IVA chemotherapy (I_RIVA) in newly diagnosed very high risk rhabdomyosarcoma: A phase Ib study within the EpSSG Frontline and Relapsed Rhabdomyosarcoma study (FaR-RMS).

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Background: Event-free survival for patients in the highest risk groups of rhabdomyosarcoma (RMS) remains poor. The COG ARST0431 study showed that dose-intensified chemotherapy benefits a subset of metastatic RMS patients. This phase Ib trial defined the safety profile, highest tested dose (HTD), and recommended phase 2 dose for dose intense irinotecan on days 8-12 combined with the standard European 3-weekly Ifosfamide, Vincristine, Actinomycin D (IVA) regimen within the European *paediatric* Soft tissue sarcoma Study Group (E*p*SSG) Frontline and Relapsed Rhabdomyosarcoma (FaR-RMS) study (ClinicalTrials.gov: NCT04625907). **Methods:** Patients aged >1 to ≤25 years with Very High Risk (VHR) RMS (FOXO1 fusion-positive, node-positive, Subgroup G and metastatic, Subgroup H) were included in designated Phase I centres. Participants received IVA (Ifosfamide 3000 mg/m² on days 1–2; vincristine 1.5 mg/m2 on days 1 and 8 and on day 15 in cycle 1 and 2 only; actinomycin D 1.5 mg/m2 on day 1 with irinotecan on days 8–12. The irinotecan starting dose was 20 mg/m²/day, with dose escalation/de-escalation to a maximum of 50mg/m2/day utilising a rolling six design. The Dose Limiting Toxicity (DLT) period was defined as up to 28 days after the start of cycle 2. All Adverse events (AEs) were assessed against the DLT definition during this time. DLTs included Grade 3 diarrhoea, enterocolitis, ileus or oral mucositis persisting > 3 days; Grade 4 diarrhoea; neutropenia or thrombocytopenia delaying treatment > 7 days; Grade 3/4 toxicities resulting in treatment discontinuation, or any Grade 5 toxicity (death) related to trial treatment. First radiological response assessment was after cycle 3 I_RIVA. **Results:** A total of 22 patients (Subgroup G, 3; Subgroup H, 19) were enrolled across 4 dose levels (20 mg/m2/day (n = 5); 30 mg/m2/day (n = 5); 40 mg/m2/day (n = 6); 50 mg/m2/day (n = 6)). Median age was 13.4 years; interquartile range, 5.2-16.3 years. All patients were evaluable for DLTs. One DLT of Grade 3 enterocolitis was observed at dose level 50 mg/m². The HTD and RP2D of irinotecan in combination with IVA were established as 50 mg/m²/day. The most common Grade 3/4 AEs occurring in > 30% of patients, during the first 3 treatment cycles were: febrile neutropenia 13 (59.1%), neutropenia 13 (59.1%); leukopenia 12 (54.5%); anaemia 10 (45.5%), and lymphopenia 7 (31.8%). The overall Response Rate (Complete or Partial Response) at first assessment was 81.8% (18/22). **Conclusions:** The RP2D for irinotecan on days 8-12 within I_RIVA was identified as 50 mg/m²/day. The intensified I_RIVA regimen is under evaluation in randomised questions, in adults and children with paediatric-type RMS, within the FaR-RMS trial in High Risk patients (IVA vs I_RIVA) and VHR patients (IVA plus doxorubicin vs I_RIVA). Clinical trial information: NCT04625907. Research Sponsor: Cancer Research UK.

10025 Rapid Oral Abstract Session

Integrated molecular characterization of pediatric soft tissue sarcomas: A report from the COG and CCDI molecular characterization initiative.

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Background: The Molecular Characterization Initiative (MCI), a partnership between the Children's Oncology Group (COG) and the NCI's Childhood Cancer Data Initiative (CCDI), provides standardized genomic profiling of tumors and germline for subjects with newly diagnosed pediatric soft tissue sarcomas (STS). Here, we report on STS patients <25 years enrolled in MCI from July 2022 to July 2023. **Methods:** MCI enrollment was offered to COG institutions through APEC14B1 (Project: EveryChild), enabling patient consent, collection of clinical data, and submission of tissue/blood samples. Bio-pathology Center centrally managed sample processing, quality control, and nucleotide extraction, while molecular assays were performed at Nationwide Children's Hospital's Institute for Genomic Medicine. Whole-exome sequencing (WES) of tumor/normal, DNA methylation arrays and RNA fusion analysis were conducted in a CLIA-certified environment. Clinical reports, except methylation results, were returned to treating institutions within 21 days, and clinical, sequencing and methylation data were deposited in NCI's Cancer Data Service. **Results:** In total, 226 rhabdomyosarcoma (RMS),158 non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and 36 non-malignant soft tissue tumors (21 desmoid tumors) from 129 institutions were enrolled. Of 172 RMS patients, 56 were fusion-positive (FP) (46 with *FOXO1* fusion and 10 with fusions of other genes). WES of 179 RMS patients identified somatic mutations in 33 genes in 110 patients (61.4%). Most frequently mutated genes included *FGFR4* [25/179,14%; FN (fusion-negative) RMS:21%, FP RMS:2%), *TP53* (21/179,12%; FN RMS:15%, FP RMS: 7%), and *NRAS* (18/179, 10%; FN RMS:14%, FP RMS: 3%). Somatic copy number variants (CNVs) were detected in 164/179 (92%) of RMS patients. Germline variants were identified in 18 of 179 RMS (10%; FN RMS:15%, FP RMS: 2%); and most commonly germline altered genes included *TP53* (4/179, 2%), *APC* (2/18, 1%), and *ATM* (2/179,1%). Among 158 NRSTS > 20 histologies were enrolled, most common being synovial sarcoma (n = 16, 8%). Of 49 patients with an initial diagnosis of undifferentiated sarcoma, round cell sarcoma, spindle cell sarcoma and sarcoma NOS, 32 underwent fusion testing, and 28 had WES: in 13 (40%) sequencing resulted in specific diagnosis [CIC::DUX4 in 5, BCOR::CCNB3 in 4, *NTRK* rearrangement in 2, SS18::SSX2 in 1 and EWSR1::ETV1 in 1], and 5 (15%) had rare fusions involving *NUTM1*, *NSD3*, *EGFR* and *COL1A1* genes;16 exhibited somatic CNVs; 5(18%) had somatic mutations; and 2 (7%) carried germline variants in *TP53* and *RET* genes. Overall, MCI results, as reported by institutions, facilitated clinical trial enrollment in 15%, receipt of targeted therapy outside trials in 17%, and diagnostic refinement in 25% of tested patients, respectively. **Conclusions:** CCDI's MCI program provides comprehensive genomic profiling of pediatric and adolescent STS, uncovering distinct somatic genetic alterations, rare fusions, actionable genomic targets and germline variants. Research Sponsor: St. Baldrick's Foundation; NCTN Operations Center Grant; U10CA180886; Statistics and Data Center Grant; U10CA098413.

10026 Rapid Oral Abstract Session

Gut microbiome changes in pediatric AML and association with event free survival.

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Background: Pediatric acute myeloid leukemia (AML) is characterized by months of hospitalization with a high risk for infections and a higher rate of relapse than many pediatric leukemias. Recent studies have highlighted the relationship between gut microbiome changes, long term cancer outcomes, and development of comorbidities. However, no study to date has examined the longitudinal changes in the gut microbiome in pediatric AML patients. **Methods:** In this retrospective study, longitudinal stool samples were taken from 14 pediatric patients with AML treated at Children's Hospital Colorado. Sample collection started after initial diagnosis for 11 patients and after first relapse for 3 patients. These samples were analyzed using 16S ribosomal RNA (rRNA) gene sequencing along with clinical data extracted via manual chart review. **Results:** We found that the relative abundance of genus *Fusobacterium* was associated with relapses. Analysis indicated that Fusobacterium was significantly elevated in the stool of 3 of 6 newly diagnosed patients who relapsed within 5 years (using a linear model that also accounted for risk stratification based on genetics and treatment response ($p = 0.03$)). These patients had elevated *Fusobacterium* at multiple timepoints during treatment. Samples from the 5 newly diagnosed patients who did not relapse showed minimal *Fusobacterium*. *Fusobacterium* has previously been associated with other cancers, oncogenesis and immune evasion. Of the 14 patients, 5 experienced 1-4 cases of *Streptococcus mitis* bacteremia (SMB) during the sample collection period. Genus *Streptococcus* abundance in stool samples collected immediately prior to SMB did not correlate with positive blood cultures, although this genus was highly prevalent in the gut microbiome of patients with repeated episodes. Using mixed effects random forest model (MERFM) to broadly survey whether changes in any other gut bacteria predicted a positive SM blood culture, we found evidence for a negative relationship between SMB and change in relative abundance of genus *Blautia*, and a positive relationship with the genera *Marvinbryantia, Anaerococcus, Parabacteroides* and *Dielma*. This suggests that other aspects of microbiome composition may influence whether *Streptococcus* can translocate into the bloodstream. Of the 14 patients, 4 developed *Clostridioides difficile* infections (CDI) during the collection period. Increases in genus *Clostridioides* relative abundance occurred prior to clinical CDI. Using MERFM, Faith Phylogenetic Diversity was negatively related to development of CDI and presence of the genera *Anarofustis, Bilophila, Alistipes* and was positively related to CDI. **Conclusions:** These results show that the gut microbiome may be implicated or serve as a prognostic indicator for relapse in pediatric AML. Additionally, longitudinal gut microbiome changes in patients may be associated with various clinical complications. Research Sponsor: None.

10027 Poster Session

New pediatric formulation of asciminib in children with chronic myeloid leukemia in chronic phase: Second interim analysis of pharmacokinetics and safety from the ASC4Kids study.

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Background: More treatment (tx) options to improve efficacy and long-term safety to minimize adverse effects on growth are needed for pediatric patients (pts) with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP). Asciminib (ASC) is the first BCR::ABL1 inhibitor that Specifically Targets the ABL Myristoyl Pocket (STAMP), approved for adults with newly diagnosed or previously treated CML-CP. The phase Ib/II, multi-center, open-label ASC4Kids study (NCT04925479) aims to identify the pediatric formulation (PF) dose (with food) leading to ASC exposure comparable to the adult formulation (AF) dose (fasted) of 40 mg twice daily (BID) and assess its safety. **Methods:** Pts aged 1– < 18 years (yrs) with CML-CP, without the T315I mutation, treated with ≥1 prior tyrosine kinase inhibitors are included. The primary objective is to characterize the pharmacokinetic (PK) profile of ASC in pediatric pts. Secondary endpoints include safety and molecular responses. In an exploratory AF group, pts 14– < 18 yrs were treated with the AF. In Part 1 (dose determination), the PF dose of 1.3 mg/kg BID was confirmed based on exposure in adult studies (40 mg BID) and no observed dose-limiting toxicities (DLTs) over the first 28 days. In Part 2 (dose expansion), additional pts are treated with the confirmed PF dose for further evaluation of exposure and DLTs (across Parts 1+2; 10 pts per group: 1– < 12 yrs and 12– < 18 yrs). In Part 3, 10 more pts will be enrolled to receive PF 2.6 mg/kg once daily (QD). This interim analysis was conducted after 10 pts in the PF 12– < 18 yrs group had completed 28 days of tx in Parts 1+2. **Results:** 19 pts were enrolled in the PF group (7 in 1– < 12 yrs and 12 in 12– < 18 yrs groups, respectively). At data cutoff (19-Aug-2024), all pts continued to receive tx. For the PF group (12– < 18 yrs), 10 pts were evaluable for PK. Averaged ASC exposure with PF 1.3 mg/kg BID was comparable to that observed in adult studies (median last measured concentration [AUClast]: 7091 vs 5130 hr*ng/mL; median maximum plasma concentration [Cmax]: 1031 vs 939 ng/mL, respectively). For all pts in the PF group, no DLTs were observed. With a median duration of exposure of 36.7 weeks, 18 pts experienced adverse events (AEs; any grade); 2 had Grade ≥3 AEs. From baseline (BL) to data cutoff for height percentile shift in the PF group; 9 pts stayed in the same percentile, 4 dropped and 6 increased. Four of 19 pts had notably low bone age at BL; 3 of these also at Week 52. At BL,16/18 pts in the PF group had *BCR::ABL1*^{IS} ≤10% and 6 were in major molecular response (MMR). Of 11 and 9 pts evaluable for efficacy at Weeks 28 and 40, 10 and 9 had *BCR::ABL1*^{IS} ≤1%, and 7 and 6 were in MMR, respectively. **Conclusions:** The confirmed PF ASC dose of 1.3 mg/kg BID was well tolerated in pediatric pts, with evidence of efficacy and no new safety signals. In Part 3, a 2.6 mg/kg dose QD will be evaluated. Clinical trial information: NCT04925479. Research Sponsor: Novartis Pharmaceuticals.

10028 Poster Session

Financial toxicity and association with treatment outcomes during pediatric CAR T therapy.

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Background: Chimeric antigen receptor T cell (CAR) therapy has revolutionized the treatment of relapsed/refractory pediatric B cell malignancies. However, the financial toxicity (FT) experienced by families is unknown despite the likely high burden imposed by clinic visits, hospital admissions, and potential travel/relocation to referral centers. We present the first report of pediatric FT among families of children receiving CAR therapy including prevalence, trajectory, and impact on outcomes. **Methods:** This is a prospective cohort analysis of patient (pt) and caregiver-reported FT outcomes for pediatric and young adult pts receiving CD19-directed CAR therapy at the Children's Hospital of Philadelphia. Caregivers (for pts $<$ 18 years old) or pts (if $\geq$ 18 years old) completed the Comprehensive Score for Financial Toxicity (COST) prior to CAR infusion (baseline), 1 month, and 3 months post-infusion. COST is a self-report FT measure that has been used in adults with specific validated grading criteria (0-3) anchored on independent differences in health-related quality of life. We described baseline FT and tested its association with treatment-related toxicity (occurrence of any cytokine release syndrome [CRS]) and outcomes (complete response [CR] at day 28) using multivariable models adjusted for time from diagnosis, prior CAR exposure, and disease burden at infusion. FT was hypothesized to impact outcomes through physiologic stress affecting immunologic response. In pts with COST data through 3 months, we described longitudinal FT trajectories. **Results:** From 9/2019-12/2024, 144 pts (33% racial/ethnic minority, 8% public insurance) or their caregivers (28% less than college degree, 22% annual household income $<$ $50,000) completed baseline COST measures. 94% of the cohort had caregiver-reported FT. 81% of pts were external referrals. The median baseline COST score was 20.0 (IQR: 11.0-29.0), which corresponds to Grade 1 FT. Two-thirds of pts reported FT, with 37%, 29%, and $<$ 1% of families experiencing grades 1-3 FT, respectively. 80% of pts had CRS; 89% had CR at day 28. Baseline FT was not associated with CRS or day 28 response (all $p > 0.2$). A subset of n = 80 had complete longitudinal data and follow up of at least 3 months. In this cohort, median COST score at baseline, month 1, and month 3 was 19.5 (IQR: 10.0-29.3), 18.5 (IQR: 11.0-27.3), 16.0 (IQR: 9.8-27.0), respectively. Strikingly, 23% and 25% of pts had clinically worse grades of FT at 1 month and 3 months post-infusion (compared to baseline), respectively. Race/ethnicity, language, insurance, caregiver education, and income were not associated with worsened FT over time. **Conclusions:** There is a high prevalence of FT at time of CAR infusion for families of pediatric and young adult pts. Reassuringly, FT at the time of infusion was not associated with two key treatment outcomes, but more investigation is needed. For a notable proportion of families, FT worsens over time and highlights the need for interventions to address cumulative financial burden. Research Sponsor: American Cancer Society.

10029 Poster Session

Growth recovery in patients with *BRAF* altered pediatric low-grade gliomas (LGG) after discontinuation of tovorafenib.

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Background: Tovorafenib is a selective, CNS-penetrant, type II RAF inhibitor that targets BRAF and CRAF. Based on preclinical data, CRAF plays an essential role in chondrocyte maturation, a required step in linear bone growth. Children treated with tovorafenib in early phase studies demonstrate a reversible decrease in growth velocity consistent with CRAF inhibition with no signs of premature closure of growth plates or adverse effects on bone such as fractures or treatment emergent osteopenia. Here we report a combined analysis of off-treatment growth recovery in patients treated with tovorafenib in 3 clinical studies. **Methods:** Patients aged < 18 years with *BRAF* altered relapsed/refractory LGG treated with tovorafenib in the Phase 1 PNOC014 study (NCT03429803), Phase 2 FIREFLY-1 study (NCT04775485), or Expanded Access Program (EAP) for patients (NCT05760586) were included. Relevant medical history, neuroendocrine medications, growth parameters, and tovorafenib dosing were collected. Pre- and post-treatment annualized growth velocity (AGV) was calculated for all patients with growth data available $\geq$90 days post-discontinuation of tovorafenib. **Results:** As of 17-Jan-2025,38/167 (23%) patients were evaluable for growth recovery. Among these evaluable patients, median age at start of treatment was 9.5 yrs (range 3.5 -16.5). Eighteen (47%) patients had a tumor associated endocrinopathy or comorbidity that may affect growth including growth hormone deficiency (8), thyroid disease (8), precocious puberty (6) and panhypopituitarism (4) at baseline. Four (11%) were receiving a gonadotropin-releasing hormone analogue for precocious puberty and 2 (5%) were receiving growth hormone replacement concurrent with tovorafenib. Median baseline height Z-score was -0.13 (range -2.57, 2.64) with 4 patients having Z-score > 2 or < -2. Median on-treatment AGV was 1.7 cm/yr [n = 36, interquartile range (IQR) 0.4 - 2.2] at 12 mo and 2.3 cm/yr (n = 25, IQR 0 - 3.3) at 24 mo. Median age at end of treatment was 11 yrs (range 4.4 - 17.5), and median off-treatment follow up was 10.3 mo (range 3.2 - 37.2). Median off-treatment AGV was 4.3 cm/yr (n = 38; IQR 1.8 - 7.6) at 3 mo, 10.2 cm/yr (n = 26, IQR 2.3 - 13.8) at 6 mo and 7.7cm/yr (n = 5, IQR 4.1 - 13.9) at 12 mo. Thirty-four (89%) patients had recovery of AGV, and 28 (74%) had an increase in Z-score towards baseline indicating catch-up growth. Patients with slow AGV recovery tended to be $>$15 years, younger females with precocious puberty/Tanner stage 4, or have only 3 months of off-treatment follow up. **Conclusions:** Decreases in growth velocity were common during tovorafenib treatment. Majority of patients to date demonstrate AGV recovery as early as 3 months with signs of catchup within 6-12 months after stopping tovorafenib. Preliminary findings indicate tumor-associated precocious puberty/Tanner stage 4 in females may be a risk factor for slow AGV recovery. Research Sponsor: Pacific Pediatric Neuro-Oncology Consortium; PLGA Fund at Pediatric Brain Tumor Foundation; Team Jack Foundation; National Cancer Institute; Day One Biopharmaceuticals.

10030 Poster Session

Cerebrospinal fluid proteome during chemotherapy for childhood leukemia: Identifying pathways associated with treatment and system toxicity.

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Background: Acute Lymphoblastic Leukemia (ALL) is the most common childhood cancer with a 5-year survival rate > 90%. Survivors treated on contemporary chemotherapy-only protocols are at heightened risk for musculoskeletal, endocrine, cardiac, and neurological/neurocognitive late-effects. Chemotherapy treatment doses and administration routes (i.e., intrathecal) are associated with the late-effects and alterations in targeted cerebrospinal fluid (CSF) proteins. We aimed to identify CSF proteome pathways linked to patient variables, treatment exposures, and early adverse events (AE). **Methods:** At diagnosis and the end of induction, CSF samples were collected from 178 ALL patients (71 females, mean age [range] 7.6 [0.5-18.8] years at diagnosis) treated on a chemotherapy-only protocol. Expression of 3188 proteins was measured via tandem-mass-tag mass spectrometry and clustered via Weighted Gene Co-expression Network Analysis (WGCNA). Severe/life threatening (CTCAE grade 3/4) AEs across multiple organ systems were compiled per patient. Trait-Cluster association was assessed by generalized linear models, linking cluster-specific eigenvalues to final treatment risk stratum (Standard/High vs Low) and AE occurrence, with false discovery rate corrected significance threshold of $p < 0.2$. Protein-Protein Interaction (PPI) network and enrichment analysis were performed by STRING within target clusters. **Results:** Patients experienced AEs in 24 organ systems (86% post-induction) and > 5% of patients experienced toxicities in 6 systems during and 11 after induction. A total of 1770 proteins were measured at both time points and WGCNA revealed 8 clusters at diagnosis (T1; 1046 proteins) and 13 after induction (T2; 1184 proteins). Four T1 clusters were associated with post-induction Hepatobiliary/Pancreas AEs ($p < 0.022$). Five T2 clusters were associated with treatment risk ($p < 0.055$) and eight were associated with AEs: Hepatobiliary/Pancreas ($p < 0.184$), Musculoskeletal/Soft Tissue ($p < 0.151$), or Neurology ($p < 0.196$). In four T2 clusters associated with both risk and AEs, PPI analysis revealed 251 pathways involved in nervous system development, skeletal/cardiac development, and immune regulation. **Conclusions:** The associations of Musculoskeletal/Soft Tissue, Neurology, and Hepatobiliary/Pancreas AEs with risk-associated clusters suggest pathological protein dynamics exacerbated by treatment intensity. These changes are reflected in different T1 and T2 cluster composition and the emergence of new clusters after induction. Associations between protein clusters, treatment risk, and AEs biologically connect treatment exposures to toxicities, providing mechanistic targets to reduce late-effects. Future work includes isolating enriched pathways and hub proteins to gain insight into specific protein dynamics contributing to AEs. Research Sponsor: None.

10031 Poster Session

Unraveling gut gram-negative antibiotic-resistant colonization dynamics in hematologic cancers: Insights from bioinformatics and immune signatures.

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Background: Infections account for ~60% of cancer-related deaths. Hematologic cancers have a 3x higher infection-related mortality than solid tumors, with resistant Gram-negative (GN) bacteria causing ~50% of bloodstream infections, highlighting the need to study the microbiome, antibiotic resistance, and infection risks. **Methods:** Stool samples from newly diagnosed hematologic cancer patients were collected at baseline, post-chemotherapy, and subsequent admission at Amir Hospital, a referral cancer center in southern Iran, to analyze microbial colonization dynamics. Patients enrolled in a 16-month observational program to investigate the correlation between clinical factors and infectious outcomes. Carbapenem-resistant and ESBL-producing were cultured on MacConkey agar with meropenem and ceftriaxone. ESBL and carbapenemase production assessed adhering to CLSI guidelines. To support our findings, we used the microbioTA database to identify highly elevated 16S rRNA expression in blood and lymph nodes of hematologic cancer patients, exploring microbiome-host interactions worldwide. We used gutMgene, GIMICA, and AMIDIS databases to explore key microbe-immune factor associations trough network centrality analysis of the immune factors. Central factors further examined in the Amir Cancer Registry datasets to assess their association with infectious events. STATA v27 used for statistical analyses. **Results:** Among 73 pediatric patients, GN drug-resistant bacteria was detected in 51 before hospitalization. *Escherichia coli* (86.6% of positive samples) and *Klebsiella pneumoniae* (9.5%) were the predominant pathogens. Drug-resistant E. coli persisted across samples, indicating gut colonization, consistent with microbioTA data showing E. coli detection at baseline and post-induction therapy. ESBL and carbapenemase-producing strains were 56.8% and 15.8%. Colonized patients had a 13.8% mortality rate, with bloodstream infections and typhlitis more common in K. pneumoniae and carbapenem-resistant strains. Previous antibiotic exposure, malignancy relapse, and colonization status were risk factors for mortality and infection. Investigation of the microbioTA database identified 10 datasets from Asia, Europe, and America revealed the detection of *Bacillus cereus* in 9 datasets, followed by E.coli (8) and Enterobacterales like *Salmonella enterica* (5) and K.pneumoniae (3), approving the high impact of E.coli worldwide. IL-4, IL-6, and TNF-α showed high centrality, with retrospective analysis linking their upregulated serum baseline levels to infection outcomes in Amir hospital datasets. **Conclusions:** Our study links GN microbial colonization, traced by elevated immune markers, to infectious complications, highlighting the need for microbiota-specific diagnostic and treatment protocols. Research Sponsor: None.

10032 Poster Session

Association of baseline clinical factors with outcomes in patients with localized Ewing sarcoma treated on frontline trials with interval compressed chemotherapy (ICC): A report from the Children's Oncology Group.

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Background: Identifying clinical and biological factors associated with outcomes in localized Ewing sarcoma (ES) will enable risk-stratified clinical trials with the goal of improved outcomes for high-risk patients and decreased treatment toxicity for low-risk patients. The specific aims of this analysis in localized ES patients were 1) to classify extraosseous (EO) primary tumors with subdivisions into deep (viscera, glands, body cavities, muscle, nerves) and superficial (cutaneous and subcutaneous) sites, and 2) to understand the relationship between baseline clinical factors (age, sex, primary tumor site, size (maximum dimension and volume)) and event-free survival (EFS). **Methods:** The analytic cohort included ES patients treated with ICC on AEWS0031 and AEWS1031. Primary tumor sites were defined as pelvic, non-pelvic, and EO (deep vs. superficial). Post-enrollment EFS was the primary endpoint. Univariate analyses used the Kaplan–Meier method (logrank test). Multivariable analyses used Cox proportional hazards models. To assess the impact of tumor volume as a continuous variable, a subgroup analysis was conducted using AEWS1031 only, as tumor volumes were collected prospectively on this study. Visual exploration of effects of continuous variables on EFS event hazard used restricted cubic splines with 3 knots. Tests were performed at the 5% level. **Results:** AEWS0031 (n = 628) and AEWS1031 Regimen B (n = 283) yielded 911 patients. In univariate analyses, difference in risk of EFS event was observed between tumor sites (P= 0.03). EO tumors had the highest estimated EFS compared to pelvic and non-pelvic (5 year EFS 84.7% vs. 72.4% and 75.9%). Superficial EO appeared to be a very low-risk group, albeit interpretations are limited by the small group size and singular event (one second malignant neoplasm among 15 patients). In multivariable analysis of the combined cohort, sex, race, and ethnicity were not prognostic. EO tumors may be associated with decreased hazard compared with non-pelvic bone primaries (HR 0.58, P= 0.07), and tumors ≥200 mL with increased hazard (HR 1.56, P< 0.01). In the subgroup analysis, tumor volume and age were prognostic and in visualizations age was non-linearly related to the hazard of EFS event, increasing until approximately 15 years. Tumor volume was non-linearly related to the hazard of EFS event and increased until approximately 400 mL. **Conclusions:** Patients with ES and primary tumors ≥200 mL continue to be at higher risk of an EFS event when treated with ICC, and EO tumors may be lower risk compared with other sites. Risk of an event appears to remain constant in ES patients ≥15 years or with primary tumors ≥400 mL. These findings should be validated in prospective trials and tumor biology integrated with clinical factors to improve risk stratification for localized ES. Research Sponsor: None.

10033 Poster Session

Demographic characteristics and survival outcomes of pediatric clear cell sarcoma of the kidney: A National Cancer Database retrospective study.

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Background: Clear Cell Sarcoma of the Kidney, CCSK, is a rare malignancy diagnosed during childhood. Compared to other pediatric renal neoplasms, CCSK is particularly aggressive due to its propensity for bone metastasis, resulting in a poorer overall survival rate. CCSK has a higher incidence in males than females. Given its rarity, investigating diagnostic patterns may reveal important epidemiological insights. This study analyzed the demographic factors in CCSK patients from the National Cancer Database (NCDB). **Methods:** A retrospective National Cancer Database (NCDB) from 2004 to 2020 analyzed patients who had a histologically confirmed diagnosis of CCSK (ICD-O-3 8964). Descriptive statistics were used to analyze Demographic factors (age, sex, race, Hispanic status, educational attainment, insurance status, facility type, distance from facility, and Charles/Deyo score). Regression analysis was utilized to interpret incidence trends. **Results:** Between 2004 and 2020, the NCBD identified 237 patients with confirmed CCSK, indicating a stable incidence rate (R^2 = 0.0043). The median age at diagnosis was 3 years old (SD = 24.83; range, 0–86). Males comprised 56% of the cohort, and 44% were females. Most patients were White (78%) and non-Hispanic (79%). Nearly all primary tumors (99%) occurred in the kidney and renal pelvis, with a median tumor size of 120 mm (SD = 42.33; range, 13–202). Over half of patients (54%) had private insurance, while 27% were on Medicaid. The majority (93%) had a Charlson/Deyo comorbidity score of 0. Most patients (99%) did not receive palliative therapy. 71% of the patients underwent a surgical procedure at the primary site, 70% received radiotherapy, and 76% received it as part of their primary treatment. Most patients (90%) lived in metropolitan areas, and they resided a median distance of 15 miles (SD = 57.1; range, 0.5-377.3) from the reporting hospital. The two-year, five-year, and ten-year survival rates were 86%, 81%, and 76%, respectively, with a mean survival of 163 months. **Conclusions:** To the best of our knowledge, this is the first NCDB analysis of CCSK, addressing a significant knowledge gap. Nearly all CCSK cases originated in the kidney or renal pelvis, consistent with literature indicating the kidney as the primary site with a stable incidence over time. These are the first socioeconomic factors of CCSK patients that have been described in the literature: CCSK patients are more likely to be white and non-Hispanic, male, have private insurance, and live in metropolitan areas. Further research is essential to better understand how demographic and socioeconomic factors influence the diagnosis, treatment choices, and overall survival of patients. Research Sponsor: None.

10034 Poster Session

Late effects in high-risk neuroblastoma survivors who received MIBG therapy.

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Background: Meta-iodobenzylguanidine radiolabeled with iodine-131 (^{131}I-MIBG) is used to treat high-risk neuroblastoma (HRNB) as monotherapy as well as in combination with other therapies, however associated late toxicities have not been well studied. The aim of this study was to describe the characteristics of HRNB survivors who received ^{131}I-MIBG and determine if ^{131}I-MIBG is associated with subsequent malignancy, growth impairment, thyroid toxicities, and other major organ (musculoskeletal, gonadal, gastrointestinal, cardiac, or pulmonary) toxicities. **Methods:** The Children's Oncology Group LEAHRN study, ALTE15N2, evaluated HRNB survivors diagnosed after 2000 and at least five years from diagnosis. Clinical history was abstracted via study questionnaires. Clinical characteristics, treatment history, and the prevalence of late effects were descriptively summarized for subjects treated with ^{131}I-MIBG (cases). Subjects who did not receive ^{131}I-MIBG therapy were randomly selected and matched by age at diagnosis and relapse history (controls) in a 1:2 case-control study design. Chi-squared analysis was used to evaluate the association between ^{131}I-MIBG and late toxicities. P-values were adjusted using the Holm-Bonferroni approach. **Results:** Of 375 subjects enrolled in LEARHN, 32 (8.5%) received ^{131}I-MIBG. Of these, 17 (53%) reported relapsed or refractory disease. Mean age at ^{131}I-MIBG treatment was 5.1 years. 56% were male. Disease extent included an adrenal primary in 62%, multiple bone metastases in 72%, and bone marrow involvement in 63%. Thyroid toxicity (hypothyroidism, hyperthyroidism, or thyroid nodules) was similar in both groups, reported in 10/32 cases compared with 11/63 controls. One case (1/32) and four controls (4/64) reported a subsequent malignancy. Growth failure was reported in 35% of cases (11/31) and 23% of controls (16/63). Other major organ toxicities were also similar with no significant differences between cases and controls. **Conclusions:** In survivors of HRNB, the burden of late toxicities appeared similar in those treated with ^{131}I-MIBG compared to those who were not. This provides critical information for long-term follow-up care and clinical trial design. Research Sponsor: Children's Oncology Group National Clinical Trials Network Statistics and Data Center; NCTN Operations Center; Grant U10CA180886; St. Baldrick's Foundation Consortium Grant; Grant No. 353158; NCORP; Grant No. UG1CA189955.

10035 Poster Session

Survival and prognostic factors of patients with Ewing sarcoma at first recurrence following modern era multimodal therapy: A report from the Children's Oncology Group (COG).

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Background: Ewing sarcoma (EwS) is a rare malignancy of children, adolescents and young adults for which outcomes have progressively improved through intensification of conventional chemotherapy, including interval compression of cycles. Prior cooperative group reports of relapsed EwS included patients treated less intensively and with fewer treatment options at relapse. Here, we report overall survival (OS) and prognostic factors post-first recurrence in patients with EwS treated with frontline interval-compressed chemotherapy. **Methods:** We included patients treated on the last three phase 3 COG EwS studies treated with interval compressed chemotherapy, which accrued from 2001-2019. Patients with initially localized disease (L-EwS) were treated on AEWS0031 arm B and AEWS1031. Patients with initially metastatic disease (M-EwS) were treated on AEWS1221. The primary outcome was OS from first relapse. Demographic and clinical data from original diagnosis and from relapse were analyzed as potential prognostic factors. Kaplan-Meier survival curves were constructed and groups compared with log-rank tests. **Results:** 366 patients experienced disease recurrence as first event and were included in this analysis (AEWS0031 arm B, n = 69, AEWS1031, n = 115, for a total of 184 with L-EwS; AEWS1221, n = 182, all with M-EwS). Median age at relapse was 16 years. Median time from initial enrollment to first relapse was 1.52 years and was shorter for patients with M-EwS (Kruskall-Wallis, $p < 0.001$). First relapses were isolated local, isolated distant, and combined in 24%, 70%, and 6.4% of patients, respectively. Metastatic stage at initial diagnosis was associated with increased risk of post-first recurrence OS event ($p < 0.0001$). Two-year OS post-first recurrence (OS_{2y}) was 25.6% for patients with M-EwS and 48.5% for patients with L-EwS. Time to first recurrence was also a predictor of post-recurrence survival ($p < 0.0001$): patients with initial L-EwS and relapse < 2 years from diagnosis had OS_{2y} of 31.4% vs. 70.8% for later relapses. Patients with initial M-EwS and relapse < 2 years from diagnosis had OS_{2y} of 18.9% vs. 71.2%. Patients with combined relapses had higher risk of post-relapse death compared to other patterns of failure ($p = 0.003$), an effect that was largely driven by the one seen in patients with initial L-EwS. **Conclusions:** Overall survival of patients with first recurrent EwS after having received modern era therapy with interval compressed chemotherapy on recent COG trials remains poor, particularly for M-EwS, early relapse and combined relapses. These data will inform the design of trials for this relapsed population and provide critical data to help counsel patients about goals of care at first relapse. Research Sponsor: NCTN; U10CA180886; NCTN; U10CA180899; St. Baldrick's Foundation; Children's Oncology Group; U10CA098543; Children's Oncology Group; U10CA098413.

10036 Poster Session

Neurocognitive outcomes following 30.6-Gy whole-ventricular radiotherapy with 54-Gy total dose focal tumor bed boost for CNS non-germinomatous germ cell tumors: A Children's Oncology Group study (ACNS1123).

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Background: COG ACNS1123 stratum 1 was a prospective, phase II trial treating children with localized non-germinomatous germ cell tumors of the brain with chemotherapy followed by whole ventricular (WV) radiotherapy (RT, 30.6 Gy) and a focal tumor bed boost (54 Gy total dose) Given the potential adverse impact of RT on survivors' neurocognitive development, ACNS1123 had a co-primary objective to evaluate and longitudinally model cognitive and behavioral outcomes. **Methods:** Cognition was prospectively examined at 9, 30, and 60-months post-diagnosis via COG protocol ALTE07C1. Attention/concentration, processing speed (PS), and estimated intelligence quotient (est. IQ) were assessed by Wechsler Intelligence tests. Survey-reported attention and executive functioning (EF) were also obtained. Multivariable linear mixed-effects models examined trends over time, as well as associations and interactions with age, gender, tumor location (pineal gland versus other) and insurance type (private versus other and private versus public). **Results:** Seventy patients were evaluable and received WVRT followed by focal RT boost. Mean age at initiation of RT was 11.8 $\pm$ 4.3 years; 74% were male. A total of 56, 60, and 61 patients had at least one valid assessment score across 3 time points for attention/concentration, est. IQ and PS, respectively. Nine, 20 and 20 patients had data at all 3 time points for attention, est. IQ and PS, respectively. The average PS scores fell below the normative mean at all three time points. The average Est.IQ was below the normative mean at 9 months only. Males had higher attention scores on average ($p < .01$), while patients with other insurance had lower attention compared to the private group ($p < .01$). For the model-estimated longitudinal trajectories and their interactions with clinical factors, younger children had declining processing speed ($p = 0.012$), females had declining est.IQ scores ($p < .01$) and patients with tumors at pineal gland had improving est.IQ scores ($p = 0.010$) over time. For survey-reported outcomes, there was no change in attention while younger children had improved EF over time ($p = 0.045$). **Conclusions:** Treatment associated with the ACNS1123 stratum 1 protocol had variable impact on patient's longitudinal neurocognitive functioning. Younger age at irradiation and female gender were risk-factors for worse neurocognitive outcomes on examiner-administered measures. Only average PS was significantly below the normative mean at all 3 times in the collective sample. Patients should be proactively monitored for cognitive and educational supportive care services. These data could potentially serve for comparison of neurocognitive outcomes in future clinical studies that modify treatment approaches; however, the notable attrition must be considered as a limitation. Research Sponsor: U.S. National Institutes of Health; NCTN Operations Center Grant (U10CA180886); U.S. National Institutes of Health; NCTN Statistics & Data Center Grant (U10CA180899); St. Baldrick's Foundation.

10037 Poster Session

Post hoc analysis of rashes reported in patients (pts) with *BRAF*-altered relapsed/refractory (r/r) pediatric low-grade glioma (pLGG) treated with the type II RAF inhibitor tovorafenib in FIREFLY-1.

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Background: Targeted therapies have become a mainstay in the treatment of pLGG. While effective, toxicities, including cutaneous adverse events (AEs), are common. Tovorafenib received accelerated FDA approval in April 2024 for the treatment of *BRAF*-altered r/r pLGG in pts ≥6 months of age based on FIREFLY-1 (NCT04775485) trial results. Maculopapular rash, dermatitis acneiform, and erythematous rash were the most commonly reported rashes (Kilburn LB, et al. *Nat. Med.* 2024). An update on the incidence, recurrence, and resolution of rash AEs in pts who received tovorafenib in FIREFLY-1 is provided. **Methods:** This post hoc analysis included 137 pts with pLGG (arm 1/registrational: 77; arm 2/extension: 60) treated with ≥1 dose of tovorafenib. Treatment-emergent rashes, graded by investigators, were grouped as maculopapular/erythematous/eczematous (M/E/E) or acneiform/pustular (A/P) (May 10, 2024 data cutoff). A rash episode included all rash events occurring over continuous days. A new rash was any subsequent episode occurring a day or more after the prior episode end date. **Results:** Median duration of tovorafenib treatment was 21.0 months (mos). 93% (128/137) of pts had a treatment-emergent rash. Of those, 59% (76) had only M/E/E rashes, 11% (14), only A/P rashes, and 30% (38), both types. As expected, A/P rashes occurred more often in pts ≥12 years of age (y/a). The rash was graded as G1 in 36% (46), G2 in 50% (64), and G3 in 14% (18) of pts. Most experienced 1 (53% [68]) or 2 (31% [40]) rash episodes. First rash episode median time to onset (TTO) was 0.43 mos, with 47% (60) G1, 41% (52) G2, and 13% (16) G3. First rash episodes resolved for 74% (95/128) of pts within a median of 2.67 mos. Resolution of first rash was more common among pts with M/E/E vs A/P rashes. Among any rash episodes (27% [58/219]) that remained unresolved, final severity was G1 (22% [48/219]) or G2 (5% [10/219]). All G3 rashes resolved. 47% (60) of pts experienced ≥2 rash episodes, of which 82% (49) were the same/lower grade episode. Of the 11 pts with a more severe second episode, 8 (73%) resolved completely. 80% (102) of pts received standard of care (SOC) treatments for rash, primarily topical steroids/antibiotics, oral antihistamines, and emollients. Only 1 (1%) pt had a rash-related tovorafenib discontinuation. 18% (23) of pts had dose interruptions due to rash. 11% (14) of pts had a dose reduction due to rash; of those, 57% (8) required no additional dose reductions due to rash. **Conclusions:** Rashes were common in pts treated with tovorafenib in FIREFLY-1. They typically occurred early in treatment, most were G1 or G2, resolved within a median of ~3 mos, and were manageable with SOC treatment and/or tovorafenib dose modifications. A/P rashes occurred more frequently in pts ≥12 y/a; there were no other significant trends in rashes experienced between the two age groups. Clinical trial information: NCT04775485. Research Sponsor: Day One Biopharmaceuticals, Inc.

Safety and efficacy of pucotenlimab combined with standard chemotherapy regimens in the neoadjuvant treatment of pediatric patients with intermediate or high-risk rhabdomyosarcoma: A phase I/II study.

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Background: Previously, we defined the pathological complete response rate (pCR) for pediatric patients with intermediate or high-risk rhabdomyosarcoma who underwent preoperative chemotherapy alone (SIOP- 2024-ID 582). In this study, we aimed to determine the effect of preoperative pucotenlimab combined with the standard chemotherapy regimen as neoadjuvant treatment on the safety and pCR of rhabdomyosarcoma. **Methods:** In this single-arm phase I/II trial (NCT06456892), patients with rhabdomyosarcoma received neoadjuvant chemoimmunotherapy with pucotenlimab combined with standard chemotherapy intravenously on the first day of each three-week cycle for three cycles. During the dose-escalation phase, patients were infused with pucotenlimab at doses of 1, 3, and 6 mg/kg respectively. The primary endpoints in phase I were dose-limiting toxicities (DLTs) as well as the evaluation of safety and tolerability. Secondary endpoints included pathological complete response (pCR), major pathological response (MPR), and survival outcomes. **Results:** Herein, we report the adverse events and pCR in the phase I study. At the time of data analysis, the survival outcomes were not yet mature. Between June 2024 and September 2024, 15 patients were enrolled and received neoadjuvant chemoimmunotherapy. Among them, 7 patients have proceeded to surgical resection. The pCR rate was 3/7 (42.9%) , and 1/7 (14.3%) patients achieved an mPR. Treatment-related adverse events of grade 3 or 4 occurred in 11 patients , which mainly due to the chemotherapy. By the safety data cutoff, no DLTs were observed in the three dose groups. Most immune-related adverse events were grade 1 or 2, including hyperthyroidism (2/15), hypothyroidism (1/15), and fever (11/15). **Conclusions:** This study demonstrates the safety and potential efficacy of neoadjuvant pucotenlimab plus chemotherapy, with an acceptable safety profile, in patients with pediatric rhabdomyosarcoma. Clinical trial information: NCT06456892. Research Sponsor: None.

Summary of safety profile of 15 patients received pucotenlimab combined with the standard chemotherapy regimen.

Adverse effects	Grade 1	Grade 2	Grade 3	Grade 4
Decreased White Blood Cell Count	0	0	2	9
Decreased Platelet Count	3	0	1	2
Toothache	1	0	0	0
Limb Pain	2	0	0	0
Abdominal Pain	4	0	0	0
Headache	2	0	0	0
Oral Pain	0	1	0	0
Taste Disorder	1	0	0	0
Dizziness	2	0	0	0
Dysphagia	1	0	0	0
Epistaxis	1	0	0	0
Fatigue	2	0	0	0
Fever	11	2	0	0
Cough	2	0	0	0
Decreased Hemoglobin Concentration	2	8	4	0
Nausea	5	0	0	0
Vomiting	5	0	0	0
Decreased Appetite	1	0	0	0
Decreased Granulocytes	0	1	0	1
Decreased Total Bilirubin	8	0	0	0
Constipation	1	0	0	0
Diarrhea	2	0	1	0
Increased Alanine Aminotransferase	3	0	1	0
Increased Aspartate Aminotransferase	1	0	1	0
Increased Bilirubin	0	0	1	0
Hyperthyroidism	2	0	0	0
Hypothyroidism	1	0	0	0
Hypoproteinemia	5	0	0	0
Increased Uric Acid	5	0	0	0
Hypokalemia	1	0	0	0

10039 Poster Session

Irinotecan, temozolomide and naxitamab plus GM-CSF (HITS) and naxitamab plus GM-CSF and ifosfamide, carboplatin, etoposide (NICE) for patients with relapsed or refractory high-risk neuroblastoma: A single center, open-label phase 2 clinical trial.

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Background: Patients with relapsed/refractory (R/R) high-risk neuroblastoma (HR-NB) have a poor prognosis, underscoring the need to explore new therapies. In this single institution, Phase 2 clinical trial (EudraCT 2020-000538-17), we evaluated the safety and efficacy of HITS and Naxitamab (NAX) in combination with ICE (NICE) in patients (pts) with R/R HR-NB with incomplete response (partial response (PR), minor response (MR), or stable disease (SD)) to HITS. **Methods:** Eligible pts received 2-4 cycles of HITS. Patients achieving a complete response (CR as per 2017 INRC) to HITS after 2 or 4 cycles had the CR consolidated with 5 cycles of NAX+GM-CSF. Patients with an incomplete response to HITS transitioned to NICE (up to 4 cycles) and those with progressive disease (PD) discontinued. CRs to NICE were consolidated with 5 cycles of NAX+GM-CSF. HITS consisted of Irinotecan 50 mg/m2/day IV from day 1-5 concurrently with temozolomide 150 mg/m2/day orally; NAX 2.25mg/kg IV on days 2, 4, 9 and 11; and GM-CSF 250 mcg/m2/day SC on days 7-11. NICE cycles consisted of NAX 2.25 mg/kg IV on days 2, 4, 9 and 11; GM-CSF 250 mcg/m2/day SC on days 7-11; ifosfamide 1.5 gr/m2/day IV from day 1-3 concurrent with etoposide 100 mg/m2/day IV and carboplatin 400 mg /m2/day IV on day 1. HITS/NICE cycles were administered out/inpatient, respectively. NAX was infused according to the Step-Up protocol. Treatment cycles were repeated every 4 weeks. Follow-up continued quarterly after end of treatment visit for up to 3 years. **Results:** From September 2020 until December 2022, 47 patients were screened and 34 enrolled. Of the 34 pts, 2 (5.9%) had primary refractory and 32 (94.1%) relapsed refractory disease. Prior treatments included chemotherapy (34; 100%); surgery (29; 85.3%); radiotherapy (17; 50%); autologous stem cell transplant (11; 32.4%); and anti-GD2 immunotherapy (15; 44.1%. 11 NAX and 4 dinutuximab beta). Of the 19 pts with an incomplete response after HITS, 13 (68.4%) received at least one cycle of NICE, and 5 completed all therapy. For HITS, the objective response rate (ORR) was 50% and best overall response (OR) was CR = 8 (23.5%); PR = 9 (26.5%); SD = 10 (29.4%); and PD = 7 (20.6%). For NICE ORR was 53.8% and OR: CR = 2 (15.4%); PR = 5 (38.5%); and SD = 6 (46.2%). No treatment related deaths occurred. All pts receiving NICE experienced grade 3-4 AEs (most frequent were pain (29.5%); urticaria (27.4 %); and thrombocytopenia (6.8%)), one leading to treatment discontinuation. **Conclusions:** Our clinical trial results suggest different chemotherapy combinations with naxitamab have the potential to rescue patients with R/R HR-NB. No unexpected toxicities were found when combining NAX with different chemotherapeutic agents. Clinical trial information: EudraCT 2020-000538-17. Research Sponsor: None.

10040 Poster Session

Pembrolizumab in pediatric participants with relapsed or refractory microsatellite instability-high solid tumors: Results from the phase 1/2 KEYNOTE-051 trial.

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Background: KEYNOTE-051 (NCT02332668) is an open-label, multicohort, phase 1/2 study evaluating pembrolizumab in children with advanced cancers. Results from participants with melanoma, PD-L1–positive solid tumors, or PD-L1–positive lymphomas showed pembrolizumab had a manageable safety profile, encouraging antitumor activity in relapsed or refractory (R/R) Hodgkin lymphoma, and limited efficacy in most other tumor types. Here, we present results from the cohort of participants with R/R microsatellite instability–high (MSI-H) solid tumors. **Methods:** Eligible participants were aged 6 months to <18 years and had advanced R/R MSI-H solid tumors determined locally by immunohistochemistry or polymerase chain reaction, measurable disease per RECIST v1.1, and a performance status of ≥50. All participants received pembrolizumab 2 mg/kg (up to a maximum of 200 mg) every 3 weeks for up to 35 doses or until other discontinuation criteria were met. The primary end points were safety and objective response rate (ORR) per RECIST v1.1 by investigator. Secondary end points included duration of response, disease control rate (DCR), and progression-free survival (PFS) per RECIST v1.1, and overall survival (OS). **Results:** Seven participants with MSI-H solid tumors were enrolled and received treatment. At the data cutoff (Jan 18, 2022), 6 had discontinued treatment and 1 was ongoing. Median age was 11.0 years (range, 3-16), 5 were female, 6 had a central nervous system malignancy (glioblastoma, n = 4; anaplastic astrocytoma, n = 1; high-grade glioma, n = 1), and 1 had an adenocarcinoma. Median time from first dose to data cutoff was 27.6 months (range, 0.3-47.5). Treatment-related AEs occurred in 3 participants; grade 3 or 4 events occurred in 1 participant and included grade 4 lymphocyte count decreased and grade 3 pyrexia. No participants died due to AEs. The ORR per RECIST v1.1 was 0% (95% CI, 0-41); the DCR was 14% (95% CI, 0-58), with 1 participant with adenocarcinoma exhibiting stable disease. Among 6 participants with a postbaseline assessment, 2 had any reduction from baseline in target tumor size, of whom 1 had a reduction of ≥30%. Median PFS was 1.7 months (95% CI, 0.4-NR); 6-month PFS was 17%. Median OS was 7.7 months (95% CI, 1.9-NR); 6-month OS was 50%. One participant with glioblastoma had a complete response at cycle 6 after initial progression, and the complete response was maintained through cycle 20. **Conclusions:** The safety profile of pembrolizumab in children with MSI-H R/R solid tumors was manageable and consistent with other tumor types. One participant with glioblastoma had a prolonged complete response after initial progression. Further evaluation of pembrolizumab in pediatric MSI-H central nervous system malignancies is ongoing. Clinical trial information: NCT02332668. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

10041 Poster Session

Socioeconomic disparities in survival outcomes among children with non-metastatic Ewing sarcoma treated on upfront Children's Oncology Group clinical trials.

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Background: Poverty is emerging as an adverse risk factor for relapse and death across many pediatric cancers. Socioeconomic disparities have not been comprehensively investigated in Ewing sarcoma. We leveraged Children's Oncology Group (COG) data to investigate socioeconomic disparities in survival outcomes in children with non-metastatic Ewing sarcoma treated on upfront phase III clinical trials from 2001-2005 and 2010-2017. **Methods:** This was a retrospective cohort study of US patients aged 0-21 years with non-metastatic Ewing sarcoma enrolled on COG AEWS0031 and AEWS1031. The analytic cohort was restricted to participants with complete data on exposures and covariates. Poverty was the primary exposure of interest, defined at the household (sole means-tested public insurance) and neighborhood (census-defined high-poverty ZIP code with ≥20% of population below 100% Federal Poverty Level) levels. Cox proportional hazards regression models evaluated associations between poverty exposures, event-free survival (EFS), and overall survival (OS) from time of trial enrollment. Multivariable models adjusted for age (as a continuous variable), sex, race/ethnicity (non-Hispanic White vs Other), initial tumor volume (≤200 ml vs > 200 ml), primary disease site (pelvic/non-pelvic/extraosseous), and assignment to interval compressed chemotherapy (yes/no). **Results:** Among 551 complete cases, 23% (n = 128) were household poverty-exposed and 19% (n = 106) were neighborhood poverty-exposed. Median age at trial enrollment was 12 years; median event-free follow-up time was 8.7 years. In multivariable models, household poverty-exposed children experienced a 52% increased hazard of EFS-event compared to unexposed children (adjusted hazard ratio [aHR] 1.52, 95% CI 1.03, 2.26, p = 0.04), and a 64% increased hazard of death compared to unexposed (aHR 1.64, 95% CI 1.03, 2.62, p = 0.04). Neighborhood poverty-exposure was not associated with increased hazard of EFS or OS event. **Conclusions:** Household poverty, as proxied by public insurance, is an adverse risk factor for EFS-event and death among children and young adults with non-metastatic Ewing sarcoma despite standardized treatment on national clinical trials. Investigation of mechanisms driving these disparities—including treatment delays and differential local control approaches—is ongoing. These data highlight an immediate need to evaluate poverty-targeted interventions alongside new therapeutic agents to improve outcomes. Research Sponsor: None.

10042 Poster Session

HLA allele, TCR V- and J-gene segment usage combinations and their association with survival in neuroblastoma.

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Background: Neuroblastoma has variable outcomes across different risk groups. In children with stage 4 neuroblastoma, five-year overall remains around 50% in high-risk children despite the emergence of anti-GD2 antibodies. T- and NK-cell infiltration is prognostic in therapy-resistant neuroblastoma, and higher HLA class I expression is linked to better overall survival (OS). In other cancers, specific HLA alleles and T-cell receptor (TCR) V, J- gene segments have been associated with survival. Thus, we conducted a retrospective study in stage 4S neuroblastoma patients to assess whether specific HLA allele, TCR V- and J-gene segment usage combinations correlated with OS in NBL. Among combinations that were associated with OS, we also identified changes in expression of immune marker genes. **Methods:** We obtained HLA allele data from exome files of the TARGET-NBL dataset using the xHLA software. The TCR recombination reads were obtained from the TARGET-NBL RNAseq files representing tumor specimens from 99 cases, utilizing a high-stringency search algorithm. The TCR recombination reads were translated, and the complementarity determining region-3 (CDR3) amino acid sequences were obtained. HLA and TCR datasets were integrated to assess OS probabilities, comparing cases with and without specific HLA allele, TCR V- or J-gene usage combinations. Significance was determined only if independent HLA allele or V- and J-gene usage assessments were not statistically significant, but significant in the corresponding HLA allele, TCR V- or J-gene segment usage combinations. HLA allele and TCR usage combinations were grouped by association with better or worse OS probabilities, and immune marker gene expression correlations were assessed via Student's t-test and Mann-Whitney U test with a Bonferroni-corrected threshold of $p = 0.00114$. **Results:** We identified 73 HLA allele, TCR V- and J-gene usage combinations with significant OS distinctions: 20 associated with improved OS and 53 with worse OS. For example, 20 TARGET-NBL cases with the HLA-DQB1*04:02 and TRAJ29 usage combination did not reach the median compared to the 1319-day OS median for all remaining cases (log-rank $p = 0.009$). Among the cases with at least one HLA allele, TCR V- or J-gene segment usage combination with improved OS, we found that the RNAseq values for the immune markers *CD4*, *CD22*, *CD38*, *RPH1*, *TNFRSF17*, and *TNFRSF13B* were upregulated, as assessed via a Mann-Whitney U analysis. **Conclusions:** Identifying specific HLA allele, TCR V- and J- gene segment usage combinations associated with survival may further indicate patients who could benefit from immunologic-boosting treatments. Studies employing functional assays, immunogenomic profiling, and targeted immune pathway analyses may advance immunotherapeutic strategies and predictive biomarkers for neuroblastoma, particularly in high-risk patients. Research Sponsor: None.

10043 Poster Session

MYC amplification and protein expression as prognostic markers in pediatric and young adult osteosarcoma.

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Background: Risk stratification in osteosarcoma relies on metastatic status and tumor necrosis after chemotherapy. Despite a complex genomic landscape, genomic biomarkers are not yet used for predicting therapy response. *MYC* amplification has previously been identified as a potential biomarker for chemotherapy resistance but studies of MYC expression are limited. This study evaluated the relationship between *MYC* amplification and protein expression and between these biologic features and survival in pediatric and young adult osteosarcoma. **Methods:** In a cohort of 93 patients with high-grade osteosarcoma, *MYC* copy number was evaluated using a targeted sequencing panel, and MYC protein expression was quantified via IHC with an H-Score. The relationship between copy number and protein expression were evaluated via spearman correlation. Amplification (AMP) was defined as > 7 copies, and high expression (EXP) as > 175 H-score. The primary outcome, overall survival (OS), was assessed using Kaplan Meier analysis (median [IQR]) for unadjusted models and cox proportional hazard analysis (HR$\pm$SE) with models adjusted for metastatic status at diagnosis. **Results:** Among the 93 patients, 64% were male, with a median age of 14 years [range: 4–29]. *MYC* AMP was present in 16 (17%) patients, high MYC EXP in 19 (20%), and both AMP + high EXP in 8 (9%) patients. Copy number status was positively correlated with expression ($r = 0.57$, $p < 0.0001$). Patients with AMP were more likely metastatic at diagnosis (75% vs 38%, $p = 0.011$) and more so for AMP + high EXP (100% vs 39%, $p = 0.0009$), but not high EXP alone (63% vs 39%, $p = 0.11$). OS was reduced for AMP compared to non-AMP (median OS: 1.3 [1.0, 2.6] vs 6.2 [2.8, 12.8] years, $p < 0.0001$; Adj HR 3.2$\pm$0.4, $p = 0.001$) and high EXP compared to low EXP (median OS: 1.5 [1.0, 3.1] vs. 6.2 [2.8, 12.8] years, $p < 0.0001$; Adj HR 5.6$\pm$0.4, $p < 0.0001$). A dose-response relationship was seen with higher copy number or expression linked to reduced OS. Compared to non-AMP + low EXP (median OS: 7.23 [3.1, 12.8] years) there was reduced OS for AMP-only/high EXP-only (median OS: 3.1 [2.0, 4.0] years, $p = 0.01$; Adj HR 2.8$\pm$0.4, $p = 0.009$) and further reduced OS for AMP + high EXP (median OS: 1.0 [0.5, 1.0] years, $p < 0.0001$; Adj HR 15.3$\pm$0.5, $p < 0.0001$). Metastasis at diagnosis predicted reduced OS compared to localized disease (median OS: 2.0 [1.0, 4.5] vs 6.2 [4.0, 12.8] years, $p < 0.0001$), but age, sex, and tumor necrosis were not associated with OS. **Conclusions:** *MYC* amplification and protein expression are positively correlated, and both independently and synergistically predict poor OS in osteosarcoma, even after adjusting for metastatic status at diagnosis. Incorporating *MYC* amplification and expression status into risk stratification may help identify patients with worse prognosis. These data also underscore the need for therapeutic approaches tailored to the genetic basis of osteosarcoma tumor biology. Research Sponsor: None.

10044 Poster Session

Updated data of efficacy and safety of luvometinib (FCN-159) in pediatric participants with neurofibromatosis type 1 from a multi-center, open-label, single-arm phase 2 study.

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Background: Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disease characterized by multiple progressive tumor and non-tumor manifestations, with abnormal activating MAPK pathway. Plexiform neurofibromas (PN) presents in 20-50% of NF1 patients (pts) and may cause serious complications. One MEK1/2 inhibitor was approved for pediatric pts with NF1-related PN in US, EU and China, but therapeutic options remain limited. Luvometinib is a highly potent selective anti-tumorigenic inhibitor of MEK1/2, potentially effective in NF1-related PN. Previous studies have confirmed that luvometinib is expected to be a targeted therapy for neurofibromatosis type 1 in pediatric patients (pts). **Methods:** This multi-center, open-label phase 2 clinical trial is to assess safety and efficacy of luvometinib in pediatric pts with NF1- related PN. The primary endpoint was objective response rate (ORR) evaluated by investigators (INV). The key secondary endpoint was ORR evaluated by Blinded independent review committee (BIRC), and other secondary endpoints include 1-year PFS and others. Preliminary findings from the phase 2 trial were previously disclosed at ASCO 2024. Here, we present the updated efficacy and safety results in pediatric participants. **Results:** As of data cut-off (September 23, 2024), 46 pediatric pts were enrolled and treated with a dose of 5 mg/m^2 (the recommended phase 2 dose according to phase 1 study). The median follow-up time was 25.1 months. ORR evaluated by INV was 60.5% (95%CI: 44.4, 75.0), and 26 pts had partial response. ORR evaluated by BIRC was 44.2% (95%CI: 29.1, 60.1), and 19 pts had partial response. 11 of 14 pts (78.6%) with tumor pain at baseline (overall tumor pain NRS≥2) decreased to 0 points. The median DOR and median PFS were still not reached. 1-year PFS rate evaluated by INV was 95.3%. 45 pts (97.8%) experienced treatment-related adverse events (TRAEs). Among these, grade ≥3 TRAEs occurred in 10 pts (21.7%), including folliculitis(4.3%), dermatitis acneiform (4.3%), blood creatine phosphokinase increased (4.3%), ejection fraction decreased (2.2%), upper respiratory tract infection (2.2%), pneumonia (2.2%), anemia (2.2%) and gastrointestinal disorders (2.2%). 2 pts (3.1%) reported treatment-related serious adverse events. 14 pts (30.4%) experienced TRAEs led dose interruption. No reported TEAE led to dose reduction, discontinuation or death. No new safety signal was observed. **Conclusions:** Overall, luvometinib was well-tolerated and demonstrated promising anti-tumor activity in pediatric participants with NF1-related PN. Long-term efficacy and safety follow-up are ongoing. Clinical trial information: NCT04954001. Research Sponsor: Shanghai Fosun Pharmaceutical Industrial Development Co., Ltd.

10045 Poster Session

MYC amplification as a prognostic biomarker in osteosarcoma: A report from the Children's Oncology Group.

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Background: Osteosarcoma is characterized by complex chromosomal alterations and genomic instability. *MYC* copy number (CN) gains are observed in 10%-60% of cases, and *MYC* amplification is associated with poor outcomes in single-center cohorts and genomic studies of relapsed or high-risk patients. This study aimed to validate the prognostic role of *MYC* amplification in a large, multi-center cohort of patients enrolled on Children's Oncology Group (COG) up-front treatment and biobanking protocols. We also assessed other genes linked to survival. **Methods:** This retrospective, IRB-approved case-control study used banked FFPE DNA from 137 osteosarcoma samples from the COG biorepository for SNP microarray (Affymetrix OncoScan). Patients were enrolled on INT-0133, P9754, AOST0331 and APEC14B1 from 1993-2024. Amplifications of *MYC, CCNE1*, *CDK4*, and the 6p21.1 locus, as well as chromosome 6, 8, 12, and 19 ploidy were assessed. Gene amplification was defined as the ratio of gene to chromosome copies (e.g. *MYC* CN/chr8 CN) $>$ 2.0. The primary outcome was occurrence of event-free survival (EFS) event. Patients were matched on metastatic status and follow-up time. Univariate conditional logistic regression models were fit for each genetic feature to obtain the odds ratio (OR) of EFS event associated with amplification (95% confidence interval (CI)) and to conduct one-sided tests for the null hypothesis OR £ 1 at the 5% level. **Results:** Sixty-five case-control pairs for *MYC, CDK4*, and 6p21.1, and 63 for *CCNE1* were analyzed. *MYC* amplification was estimated to have a 1.87-fold increase in odds of EFS event (95% CI: 0.79, 4.42; p = 0.08). *CDK4* amplification was associated with a 5-fold increase in odds of event (95% CI: 1.10, 22.82; p = 0.02). Neither amplification of 6p21.1 or *CCNE1* were associated with increased odds of event, with ORs of 1.33 (95% CI 0.56, 3.16; p = 0.26) and 0.73 (95% CI: 0.29, 1.81; p = 0.25), respectively. **Conclusions:** *MYC* amplification may be associated with increased odds of EFS event in this cooperative group cohort. Though the result did not reach statistical significance, this finding aligns with prior studies demonstrating increased EFS-event risk for patients with *MYC* amplification. While our selection of a ratio cut point $>$ 2.0 to define amplification was informed by prior studies, the optimal cut point has not been determined and cut points may be assay dependent. Although *CDK4* amplification appears associated with increased odds of event, confidence in this finding is limited by a sparse-data bias, due to a low number of control patients with *CDK4* amplification. Future analyses will explore *MYC* and *CDK4* copy number ratio as a continuous variable and assessing the relationship between additional genomic features and EFS events in this population. Research Sponsor: Children's Oncology Group.

10046 Poster Session

A phase I dose-escalation study to assess the oncolytic virus VCN-01 safety and efficacy in refractory retinoblastoma patients.

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Background: Preclinical work demonstrated antitumor activity of VCN-01 (oncolytic adenovirus targeting the E2F pathway and expressing hyaluronidase) for retinoblastoma. We report this first-in-children study aiming to assess its safety and efficacy. **Methods:** Patients with intraocular retinoblastoma who failed conservative therapy facing imminent enucleation were eligible for this phase I, dose-escalation study (NCT03284268) with two dose levels of VCN-01 intravitreal injection (2E+9 vp/eye per dose for the first patient) and 2E+10 vp/eye dose in two doses every two weeks for the remaining 8. Dose limiting toxicity (DLT) was defined as ≥ grade IV ocular toxicity or ≥ grade III systemic toxicity according to CTCAEv04. Response assessed by RB-RECIST criteria and toxicity were evaluated at day 42 of the first injection. **Results:** Thirteen patients (4 screening failures) were enrolled. Out of the 9 treated patients, five had bilateral retinoblastoma. There was no DLT. 7/9 patients experienced adverse reactions. being uveitis the most common (7/9 patients, G3 in four). From the second patient onwards, all patients received pre-emptive oral and/or topical steroids to prevent uveitis. Uveitis was improved or resolved at day 42 in 7 patients. One patient with G3 uveitis did not receive the second dose because of medical decision and also experienced glaucoma requiring treatment. No systemic toxicities occurred. VCN-01 caused reversible changes in electroretinograms due to turbidity. Viral particles were not found in the healthy retina in enucleated eyes. No VCN-01 genomes in peripheral blood were detected in any case. At 42 days of the first injection, 5 patients achieved partial response, 3 stable disease and one progressive disease. Subsequent eye-conservative treatment was administered to 5 patients and 3 eyes are preserved with vision (follow-up 12-49 months). The remaining 6 eyes were enucleated because of refractory tumor. No extraocular relapse occurred. **Conclusions:** VCN01 was safe, being uveitis the most common adverse effect. VCN-01 did not cause retinal toxicity. The response in these heavily pre-treated eyes was encouraging. Clinical trial information: NCT03284268. Research Sponsor: None.

10047 Poster Session

Multi-omics evaluation of relapsed pediatric cancers: What information do these sequential analyses yield?

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Background: While cure rates for children with cancer have significantly improved, relapses remain a challenge, requiring deeper understanding to address them. Nowadays, genomic analyses are widely used at diagnosis and in relapse settings, becoming a standard-of-care in pediatric. The aim of this study is to describe the genomic evolution of relapsed pediatric tumors in search of clonal selection and pathway identification. We also want to assess the clinical value of these new data obtained in relapsed tumors. **Methods:** This is a retrospective analysis from canadian pediatric oncology precision medicine projects. We selected patients aged < 30 years with sequencing data available at diagnosis and relapse. Clinical and genomic data were collected, and each patient was paired with a non-relapsed patient. The incidences of genomic alterations were compared in the two populations and for each patient. For patients who relapsed, patient-adjusted longitudinal mixed models assessed differentially expressed genes at relapse vs diagnosis. Gene set enrichment analyses were performed, using GLMMSeq results, to study metabolic pathways that undergo significant dysregulation over time ($p < 0.05$). Electronic surveys were sent to the treating physicians of relapsed patients. **Results:** A total of 45 patients with 1 or more relapses were compared with 44 patients without relapse. Longitudinal analysis was performed on 35 relapsed patients. Our population has a median age of 10 y.o., a majority had leukemia (47 %) or sarcoma (31%). Among relapsed patients, the mutational burden at diagnosis was 0.82 mut/MB and 1.21 mut/MB at first relapse, compared with 0.47 mut/MB in non-relapsed patients ($p = 0.02$). 33% of relapsed patients had or acquired a TP53 alteration, compared with 16% without relapse ($p = 0.084$). MAPK pathway alterations were more prevalent among relapsed patients ($p = 0.004$). Longitudinal analyses showed enrichment in MAPK pathway at relapse. Other pathways were also significantly enriched at relapse (Wnt, TP53, TNFa, TGFb), while immune pathways (immunoglobulin/lymphocyte complex and activation) were downregulated. Although, 45% of clinicians considered that genomic analysis at relapse was useful, only 18% actually integrated the genomic data into clinical decisions due to better options available than targeted therapies. Indeed, when targeted therapies were used as proposed, it was mostly for a 2^{nd} or 3^{rd} relapse and for sarcoma. **Conclusions:** This study describes the evolution of the genomic landscape, showing an enrichment in mutation and pathways, and increased mutational burden in relapsed pediatric tumors. Longitudinal differential analyses brought more information about genomic evolution than the usual genomic reports sent to clinicians. Overall, the analyses performed are useful for clinicians, and a small subset of patients benefited from this information to guide therapies. Research Sponsor: None.

10048 Poster Session

Efficacy, safety and pharmacokinetics (PK) of zurletrectinib, a next-generation pan-TRK inhibitor, in pediatric and adolescent patients (pts) with NTRK fusion-positive (NTRK+) solid tumors.

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Background: NTRK gene fusions are significant oncogenic drivers in pediatric tumors (e.g. infantile fibrosarcoma). Zurletrectinib is a highly selective next-generation TRK inhibitor. Preclinical data of zurletrectinib showed strong activity against resistant mutations, e.g., G595R. Promising efficacy was observed in a phase I/II clinical trial (NCT04685226). The pivotal phase II clinical trial (NCT05745623) is currently ongoing. Here we report an integrated analysis by combining pediatric and adolescent pts from the two clinical trials. **Methods:** Eligible pts with locally advanced or metastatic solid tumor harboring NTRK fusions, who failed from standard of care or for whom there was currently no effective therapy were included in the efficacy analysis. Adolescent pts (12-18 years) received zurletrectinib tablet at fixed dose, and pediatric pts ($<$ 12 years) received zurletrectinib orally disintegrating tablet (ODT) based on body surface area (BSA). The primary endpoint was confirmed objective response rate (ORR) per independent review committee (IRC). Tumor responses were assessed by IRC and investigators per RECSIT1.1 and RANO (BM) criteria. Treatment-emergent adverse events (TEAEs) were evaluated and graded according to CTCAE v5.0. **Results:** As of 23 Nov 2024, 18 pts in total were enrolled, including 8 pediatric pts and 10 adolescent pts. Median age was 5.0 (range: 3-9) and 13.5 (range: 12-15) respectively. ECOG performance status was between 0-1. Among the 18 pts, 6 TRK inhibitor treatment-naïve pts with central lab confirmed NTRK+ were efficacy evaluable. The confirmed ORR assessed by IRC was 100% (95% CI 54.1, 100.0). All of the pts achieved partial response (PR) at the 1st tumor assessment and maintained the remission as of the cutoff date. Median time to response were 1.0 month (95% CI: 0.99, NE) in adolescent pts and 0.9 (95% CI: 0.89, NE) month in pediatric pts. It is worth noting that one pediatric patient who progressed on prior first-generation TRK inhibitor achieved complete response after receiving zurletrectinib. The most common treatment related adverse events (TRAEs) were ALT increased (n = 8) and anemia (n = 6), the majority of which were Gr 1 or 2. There were no TRAEs leading to dose reduction or discontinuation, and no serious TRAEs were reported. PK results indicated that zurletrectinib PK profiles in pediatrics and adolescents at the recommended phase 2 dose (RP2D) were similar to that in adults. **Conclusions:** The integrated analysis demonstrated that zurletrectinib had significant efficacy and good safety profile in pediatric and adolescent pts with NTRK+ solid tumors. Zurletrectinib also showed the potential to overcome the resistance to 1st generation TRK inhibitors. These findings support zurletrectinib is a better treatment option for NTRK+ pediatric and adolescent pts. Clinical trial information: NCT04685226. Research Sponsor: Beijing InnoCare Pharma Tech Co., Ltd, Beijing, China.

10049 Poster Session

Phase I study of mitoxantrone hydrochloride liposome in relapsed and refractory pediatric tumors.

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Background: Compared with solvent-based mitoxantrone, mitoxantrone hydrochloride liposome has been found to reduce bone marrow toxicity. This open-label, single-arm phase I clinical trial was designed to evaluate the safety and efficacy of mitoxantrone hydrochloride liposome monotherapy in the treatment of pediatric tumors. **Methods:** To explore the maximum tolerated dose (MTD) of mitoxantrone liposome in pediatric cancer patients, using a "3+3" design, patients received three dose levels (16mg/m^2, 20mg/m^2, 24mg/m^2, d1) of mitoxantrone hydrochloride liposome monotherapy every 3 weeks. Patients were observed for dose-limiting toxicity (DLT) during the first cycle. The primary endpoint was MTD, and the secondary endpoints included objective response rate (ORR) and disease control rate (DCR), DLT, adverse events (AE), etc. **Results:** From October 2022 to September 2023, total of 7 pediatric cancer patients were enrolled and completed treatment, of which 6 patients received 16mg/m^2 and 1 patient received 20mg/m^2 mitoxantrone liposome monotherapy. The median age of the patients was 13.0 years (range: 8.0, 17.0). The tumor types included soft tissue sarcoma, hepatoblastoma, T-cell lymphoma, etc. The median number of treatment cycles was 2.0 (range: 1.0, 6.0). 1 patient (16mg/m^2 dose group) developed DLT, which was a grade 3 febrile neutropenia lasting more than 7 days after G-CSF. All patients could be evaluated for toxicity, and 5 patients could be evaluated for efficacy based on imaging findings. The AE of all grades with high incidence (≥50%) were white blood cell decreased (85.7%), anemia (71.4%), neutrophil count decreased (71.4%), platelet count decreased (57.1%), and anorexia (57.1%), respectively. The overall safety was acceptable. Six patients (85.7%) discontinued treatment early, of which 3 (42.9%) were due to disease progression confirmed by imaging, and 3 (42.9%) were due to limited efficacy considered by the investigators. The overall ORR and DCR were 20% (95%CI: 0.5%-71.6%) and 40% (95%CI :5.3%-85.3%), respectively. After the observation of 7 patients, the investigators thought that the efficacy of mitoxantrone liposome monotherapy was not as expected, and the study protocol was revised to continue the study of mitoxantrone liposome combined therapy. **Conclusions:** Mitoxantrone liposome has an acceptable safety profile in pediatric cancer patients, but the preliminary efficacy is not up to expectations, and further studies on combination therapy are needed. Clinical trial information: NCT05620862. Research Sponsor: CSPC Ouyi Pharmaceutical Co., Ltd.

10050 Poster Session

Updated efficacy and safety of entrectinib in children with extracranial solid or primary central nervous system (CNS) tumors harboring *ROS1* fusions.

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Background: Entrectinib is a TRK and ROS1 inhibitor that has shown rapid and durable responses in children with *NTRK1/2/3* or *ROS1* fusion-positive (fp) extracranial solid or primary CNS tumors in an integrated analysis of the STARTRK-NG (NCT02650401), TAPISTRY (NCT04589845) and STARTRK-2 (NCT02568267) trials. These data led to FDA and EMA approval of entrectinib in pediatric patients > 1 month with NTRK fp tumors. Here we present updated data on pediatric patients with ROS1 fp tumors based on the trials listed above to further describe the efficacy and safety of entrectinib in this population. **Methods:** Eligible pts were TRK/ROS1 inhibitor-naïve, < 18 years old, with locally advanced/metastatic extracranial solid or primary CNS tumors, with measurable or evaluable-only disease. All pts who received ≥1 daily dose of oral entrectinib are included in the safety-evaluable population. Pts who had a ROS1 fusion and were followed for ≥6 months are included in the ROS1 efficacy-evaluable population. Pts received entrectinib until disease progression, unacceptable toxicity, or consent withdrawal. Tumor responses were confirmed by blinded independent central review (BICR) per RECIST v1.1 or RANO criteria. Primary endpoint: confirmed objective response rate (ORR) per BICR. Key secondary endpoints: ORR in pts with baseline measurable disease per BICR; duration of confirmed response (DoR); time to confirmed response (TTR); clinical benefit rate (CBR); progression-free survival (PFS); overall survival (OS); safety. **Results:** At clinical cut-off (16 July 2024), of the 113 safety-evaluable pts, there were 26 pts in the *ROS1* efficacy-evaluable cohort. ORR was 69.2% (95% CI 48.2, 85.7). Median TTR was 1.84 months. Median OS was not evaluable. Median duration of survival follow-up was 29.4 months (range 1–80). Efficacy outcomes are shown in the table. The most common related adverse events were weight gain (37.2%), anemia (36.3%), and AST increase (26.5%). Related fracture events occurred in 23% of pts. **Conclusions:** Entrectinib yielded rapid and durable responses in pediatric pts with *ROS1* fp extracranial solid or primary CNS tumors. The safety profile of entrectinib was consistent with previous reports. Clinical trial information: NCT02650401; NCT04589845; NCT02568267. Research Sponsor: F. Hoffmann-La Roche Ltd.

Efficacy	*ROS1* (N=26)
Confirmed ORR*, N, % [95% CI]	18, 69.2 [48.2- 85.7]
Complete response	4, 15.4 [4.4- 34.9]
Partial response	14, 53.8 [33.4- 73.4]
Median confirmed DoR*, months (95% CI)	NE (16.2- NE)
Median TTR*, months (range)	1.84 (1.6- 4.0)
CBR*, % (95% CI)	84.6 (65.1- 95.6)
Median PFS*, months (95% CI)	NE (21.8- NE)
Median OS, months (95% CI)	NE (NE- NE)

*Per BICR; CI, confidence interval; NE, not evaluable.

10051 Poster Session

A phase 1 trial of the FACT inhibitor CBL0137 in pediatric patients with relapsed or refractory solid and CNS tumors: A report from the Children's Oncology Group study PEPN2111.

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Background: CBL0137 is a novel agent that targets the FAcilitates Chromatin Transcription complex (FACT), a histone chaperone that regulates chromatin remodeling during transcription, replication, and DNA repair. CBL0137 has been shown to have anti-tumor activity in multiple preclinical models of pediatric cancer. We report the phase 1 trial of CBL0137 in children with relapsed or refractory solid tumors including central nervous system (CNS) tumors or lymphoma (NCT04870944). **Methods:** Patients (age 12 months to 21 years) with relapsed/refractory solid tumors, central nervous system tumors or lymphoma were eligible. In the dose escalation phase, a rolling-six design was used to evaluate CBL0137 administered intravenously (IV) once per week on Days 1 and 8 of a 21-day cycle. The starting dose was 400 mg/m^2, with escalation to the adult phase 2 dose (RP2D) of 540 mg/m^2. The maximum tolerated dose (MTD) was determined based on cycle 1 dose limiting toxicity (DLT) using Common Toxicity Criteria for Adverse Events (v5). Pharmacokinetics (PK) and cytokine analyses were performed during cycle 1. Seven additional patients ($<$ 18 years old) were accrued to a PK expansion cohort at the RP2D. **Results:** Sixteen patients were enrolled; 14 were evaluable for DLT assessment (12 at 400mg/m^2 [6 in dose escalation and 6 in PK expansion] and 2 at 540mg/m^2). The median (range) age was 10 (4-20) years. Diagnoses included high grade glioma (n = 6), osteosarcoma (n = 5), ependymoma (n = 2), neuroblastoma, hepatoblastoma and Burkitt's lymphoma (1 each). One of 12 evaluable patients treated at 400 mg/m^2 experienced a DLT: Grade 3 photosensitivity. At 540 mg/m^2, the two evaluable patients both had fever and dose limiting Grade 3 hypotension. Non-dose limiting Grade 3-4 toxicities included anemia, lymphopenia, neutropenia, thrombocytopenia, hypokalemia, anorexia, photosensitivity and fever. For both dose levels, a total of 12 patients were reported to have at least one episode of Grades 1-3 fever and/or Grade 1 cytokine release syndrome (CRS). PK parameters (mean$\pm$SD) for CBL0137 (400 mg/m^2) were T_{max}= 0.7 $\pm$ 0.5 h, C_{max}= 1310 $\pm$ 417 ng/mL, and AUC_{0-24h} = 15300 $\pm$ 6790 h·ng/mL. Given the unexpected toxicities of fever, hypotension, and CRS, cytokine samples were collected in patients enrolled in the PK expansion cohort; all had Grade 1 CRS and significantly elevated levels of both IL-10 (adj p = 0.001) and IL-1RA (adj p $<$ 0.001) at 24 hours vs pre-infusion. **Conclusions:** The RP2D and MTD of CBL0137 in children and adolescents with solid or CNS tumors is 400mg/m^2 IV weekly on Days 1 and 8 of 21-day cycles. CBL0137 leads to immune activation, with cytokine elevation and the possibility of CRS, an unexpected toxicity not previously reported in adults. A Phase 2 cohort in patients with Diffuse Midline Glioma is ongoing and includes further assessment of immune activation. Clinical trial information: NCT04870944. Research Sponsor: Cookies for Kids' Cancer; National Cancer Institute; UM1CA228823.

10052 Poster Session

Factors associated with survival following relapse of high-risk neuroblastoma: A study from the International Neuroblastoma Risk Group (INRG) Data Commons.

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Background: Outcomes for high-risk neuroblastoma (HR-NBL) following relapse are poor, although there is a paucity of data on overall survival post-relapse (OSPR) in the contemporary era. Prognostic factors associated with OSPR across all neuroblastoma risk groups (INSS stage, MYCN status and time to first relapse) have previously been described. Here we present an analysis focussed specifically on HR-NBL. **Methods:** We conducted a retrospective analysis using INRG Data Commons including HR-NBL patients diagnosed ≥1985 with relapse/progression ≤2022. HR-NBL was defined as age ≥547days at diagnosis with INRGSS M; or INRGSS L2 MYCN-amplified disease. The final cohort excluded patients without relapse/progression and with death as first event. Primary endpoint was OSPR, with Kaplan-Meier estimates of survival and sub-group comparisons using log-rank tests. **Results:** Of the 25,245 NBL patients in the INRG Data Commons, 4045 were included in the final analysis. The majority had INRGSS M disease (96%) and were < 5 years at diagnosis (74%), with MYCN amplification in 36% of those with available data. OSPR was 22±0.7% at 2 years and 8±0.4% at 5 years, with median OSPR 0.76 years (95% CI: 0.73-0.82). OSPR improved over time; for example, 2-year OSPR was 16+/-2.8% for patients diagnosed 1985-1989 vs 32%±2.8% for 2015-2019 ($p < 0.0001$). Across the whole cohort, patients with a diagnosis of NBL (vs nodular ganglioneuroblastoma), greater number of involved metastatic compartments (MSI) or elevated LDH at diagnosis, tumors with MYCN amplification, higher MKI, 1p LOH and presence of ALK mutation had statistically significantly worse OSPR than respective counterparts. OSPR for INRGG M was significantly better than for INRGSS L2. Serum ferritin, tumor grade and ploidy were not associated with OSPR, while 11q LOH and age showed non-proportional hazards, with patients aged ≥5 years at diagnosis having a better early OSPR but poorer long-term outcome than those < 5 years. **Conclusions:** In this, the largest analysis of patients with relapsed HR-NBL, multiple factors at diagnosis were associated with OSPR, emphasising the importance of tumor biology and disease burden. The finding of improved OSPR for INRG M vs L2 is unexpected but may relate to MYCN amplification. Further analyses will focus on changes in prognostic factors over time, non-proportional hazards and the impact of upfront and relapse treatment paradigms on OSPR and prognostic factors. Research Sponsor: Garron Family Cancer Centre.

Whole genome-based circulating tumor DNA analysis as an ultrasensitive biomarker in pediatric sarcomas.

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Background: Disease monitoring in pediatric sarcomas relies on invasive surgical biopsies and radiologic imaging, which often trail disease activity. Circulating tumor DNA (ctDNA) is an attractive potential biomarker, but studies in pediatric sarcomas have reported low detection rates by tracking copy number alterations or recurrent genetic alterations. We aim to establish a personalized ctDNA pipeline in pediatric sarcomas based on identification of tumor-specific single nucleotide variants (SNVs) from whole genome sequencing (WGS) to enhance ctDNA detection. **Methods:** Patients < 25 years old with new or relapsed sarcoma treated at our institution are eligible to enroll in our study, which is ongoing. Plasma is collected at imaging response evaluations. Matched tumor and germline DNA are collected at baseline and undergo paired WGS to identify tumor-specific SNVs, and personalized hybrid capture panels are designed to track up to 5000 mutations per patient. Cell-free DNA from each time point is analyzed with CAncer Personalized Profiling by deep Sequencing (CAPP-Seq) using duplex sequencing to minimize the background error rate and maximize sensitivity. **Results:** This approach was piloted in 8 pediatric patients with osteosarcoma (5), Ewings sarcoma (2), and rhabdomyosarcoma (1). A median of 619 tumor-derived SNVs (range 160-4937) were tracked per patient. ctDNA was detected in all patients at baseline with mean allele fractions ranging from 0.000937-27.1. Table 1 summarizes characteristics, number of SNVs tracked, and mean allele fraction for each patient. Seven patients had longitudinal ctDNA samples available for analysis. In all patients, ctDNA broadly correlated with radiologic response with ctDNA becoming undetectable in patients with an imaging response and ctDNA remaining detectable in patients who experienced progression. One patient achieved initial remission with undetectable ctDNA and relapsed with ctDNA re-emergence. **Conclusions:** Personalized whole genome-based ctDNA analysis may improve ctDNA detection in pediatric sarcomas. In this pilot, ctDNA was detected at baseline in 8/8 patients, and ctDNA levels correlated with treatment response on imaging. A personalized approach for ctDNA detection in pediatric sarcomas has the potential to aid in disease monitoring and treatment selection. Research Sponsor: Conquer Cancer, the ASCO Foundation; Stanford Maternal and Child Health Research Institute; Dianne Taube Family Foundation.

Patient characteristics and baseline ctDNA allele fraction.

Disease	New (N) v Relapsed/ Refractory (R)	Localized (L) v Metastatic (M)	Sex (M, F)	Age (years)	SNVs (n)	Baseline ctDNA Mean Allele fraction
Osteosarcoma	N	L	M	17	692	0.25
Osteosarcoma	N	L	M	14	301	4.29
Osteosarcoma	R	M	M	20	4937	0.00094
Osteosarcoma	R	M	F	11	1684	27.10
Osteosarcoma	R	M	M	12	546	2.70
Ewings sarcoma	N	L	M	5	160	14.11
Ewings sarcoma	N	L	M	6	198	0.78
Rhabdomyosarcoma	R	M	F	19	935	2.79

Each row represents 1 patient with disease and ctDNA detection characteristics displayed.

10054 Poster Session

A phase 2 study of sirolimus in combination with metronomic chemotherapy (CHOAnome) in children with recurrent and/or refractory solid and CNS tumors.

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Background: Outcomes for recurrent and/or refractory (R/R) solid and central nervous system (CNS) tumors remain poor. Sirolimus, an mTOR inhibitor, has both antiproliferative and antiangiogenic effects, and the mTOR pathway is activated in many cancers. Low-dose metronomic chemotherapy also decreases neovascularization and has demonstrated activity in many pediatric tumors. We previously conducted a phase 1 trial establishing the dose (2 mg/m^2), safety and tolerability of sirolimus in combination with metronomic chemotherapy. The current study is a prospective, multi-institutional phase 2 trial to determine the objective response rate (ORR) in children with R/R solid and CNS tumors treated with this regimen (NCT02574728); herein we report the results of the solid tumor stratum. **Methods:** Patients aged 12 months to 30 years with R/R extracranial solid tumors were eligible. Patients were required to have measurable disease and no known curative therapeutic options. Treatment consisted of continuous sirolimus (2 mg/m^2/dose PO daily), celecoxib (100 mg PO BID), and oral etoposide (50 mg/m^2/day; max: 100 mg) alternating every 21 days with oral cyclophosphamide (2.5 mg/kg/day; max: 100 mg) in 42-day cycles. Sirolimus was dose-adjusted to maintain a serum trough concentration of 10-15 ng/ml. Response was determined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Enrollment proceeded using a Fleming's two-stage design based on best overall response (BOR), requiring 2 objective disease status determinations. **Results:** Twenty-four solid tumor patients were enrolled; 20/24 were evaluable for response. Median age was 14.6 years (range: 2.5–20.5); 9 (45%) were female. Diagnoses included desmoplastic small round cell tumor (DSRCT; n = 3), osteosarcoma (n = 4), Wilms tumor (n = 2), neuroblastoma (n = 5), and one each of Ewing sarcoma, rhabdomyosarcoma, CIC-rearranged sarcoma, clear cell sarcoma-like tumor of the GI tract (CCST), juvenile xanthogranuloma (JXG), and hemangiopericytoma. Median number of cycles was 2 (range: 1-13). Best response after any cycle was partial response (PR) in 2 (CCST and JXG), stable disease (SD) in 8, and progressive disease (PD) in 10 for an objective response rate of 10%. BOR was PR in 2 (10%), SD in 5 (25%), PD in 11 (55%), and unknown in 2 (10%). Median PFS was 3.6 months (range: 1.0-26.2) and median OS was 15.5 months (range: 1.0-55.4). One-year PFS was 26.2% [95% confidence interval (CI): 11.9-57.8%) with 1-year OS of 59.6% (95% CI: 35.1-77.4%). Six patients had ≥SD for ≥6 months [CCST (n = 1), DSRCT (n = 1), JXG (n = 1), hemangiopericytoma (n = 1), and neuroblastoma (n = 2)]. **Conclusions:** The combination of sirolimus with metronomic chemotherapy showed limited activity in patients with R/R solid tumors, although prolonged disease stabilization was seen across multiple histologies consistent with a metronomic approach. Clinical trial information: NCT02574728. Research Sponsor: Cannonball Kids' Cancer Foundation; Hyundai Hope on Wheels; Carter Samuel Martin Innovative Therapy Research Fund.

10055 Poster Session

Association of neurocognitive impairment and financial hardship in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS).

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Background: Adult survivors of childhood cancer are at high risk for financial hardship due to the cumulative lifetime costs of cancer-directed therapy and chronic health conditions. Whether neurocognitive impairment increases the risk for financial hardship is unknown. **Methods:** Childhood cancer survivors ($\geq$ 5-year survivors, diagnosed $<$ 21 years of age between 1970-1999) enrolled in CCSS completed a validated self-report Neurocognitive Questionnaire (NCQ) in 2014 and a subsequent financial hardship survey (age $\geq$ 26 at survey completion) 3 years later. The NCQ measured neurocognitive impairment in four domains: (1) memory; (2) task efficiency; (3) organization; (4) emotional regulation. NCQ was the exposure and operationalized as the number of impaired domains (0-4); in each domain, impairment was defined as a Z-score $>90^{th}$ percentile. Financial hardship outcomes were measured in behavioral (e.g., delaying care due to cost), material (e.g., high out-of-pocket costs), and psychological (e.g., worry about financial situation) domains, as well as two discrete outcomes of debt collection and bankruptcy. Multivariable linear and logistic regressions were used to analyze associations adjusting for age, sex, and race/ethnicity. **Results:** 3023 survivors completed the NCQ (mean age 38.8, SD=8.6 years) and a subsequent financial hardship survey (mean age 41.5, SD=8.7 years). 13.9%, 8.1%, 6.0%, and 2.6% of survivors had neurocognitive impairments in 1-4 domains, respectively. Individuals with NCQ impairment had significantly higher mean standardized scores across all three financial hardship domains than those without NCQ impairments (Table). Each ordinal increase in the number of impaired NCQ domains was associated with a higher mean standardized score for both behavioral and material financial hardship. Individuals with impairments in all four NCQ domains were more likely to be sent to debt collection (54% vs. 25%, OR=3.82, 95% CI: 2.27-6.43) and file for bankruptcy protection (21% vs. 8%, OR=2.81, 95% CI: 1.53-5.17) compared to those without impairments. **Conclusions:** Cancer survivors with neurocognitive impairment are particularly vulnerable to financial hardship. This survivor population should be specifically assessed for these outcomes and offered support to prevent and mitigate financial challenges. Research Sponsor: Childhood Cancer Survivor Study; National Cancer Institute; CA21765, C. Roberts, Principal Investigator; American Lebanese-Syrian Associated Charities (ALSAC).

Standardized mean differences (SMD) of each financial hardship domain by number of NCQ impairments compared to no NCQ impairments.

Number of NCQ domains impaired	Behavioral Domain SMD (95% CI)	Material Domain SMD (95% CI)	Psychological Domain SMD (95% CI)
1	0.21 (0.11-0.31)	0.20 (0.10-0.29)	0.41 (0.31-0.50)
2	0.39 (0.27-0.51)	0.32 (0.20-0.44)	0.38 (0.25-0.50)
3	0.48 (0.34-0.63)	0.35 (0.20-0.49)	0.44 (0.30-0.58)
4	0.72 (0.51-0.93)	0.72 (0.52-0.94)	0.74 (0.53-0.94)

10056 Poster Session

Psychologic distress amongst adolescent and young adult cancer survivors' and parents.

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Background: Increasing survival in adolescent and young adult (AYA) cancer patients has led to a growing population at risk for poor psychological outcomes. We sought to identify risk factors for the development of psychologic distress and post-traumatic stress (PTS) in AYA survivors and their parents. **Methods:** In a single-institution prospective cohort study, survivors ages 10-25 years old completed a self-report review of systems (ROS) and psychosocial surveys at initial and follow up visits, including the Youth (YSR) or Adult Self Report (ASR) assessing psychologic distress and the Impact of Events Scale (IES) assessing PTS. Parents of patients ages 10-18 years completed the Childhood Behavior Checklist (CBCL) assessing their child's psychologic distress. Parents completed the Beck Anxiety (BAI) and Depression (BDI) Index and IES assessing their personal anxiety, depression, and PTS. Psychologic distress and PTS were defined dichotomously with an internalizing problems T-score $\geq$ 60 on YSR/ASR/CBCL and IES $\geq$ 24, respectively. Psychologic distress and PTS were further analyzed as continuous variables in multivariable linear regression models with age, diagnosis, gender, time from end of therapy (EOT), substance use, sexual dysfunction, ROS, and therapy intensity. Spearman correlation coefficients were computed to assess relationships between patient and parent scores. **Results:** The study enrolled 135 patients and 72 parents, of which 37 were parents of 10-18-year-olds. Median age of patients at diagnosis was 15 years and median time from EOT was 3.2 years. 50% were female, 65% had a hematologic malignancy, and 92% were white. 20% of patients reported psychologic distress. 17% of patients and 17% of parents reported PTS. 10% and 13% of parents reported at least moderate anxiety and depression, respectively. In multivariable regression analyses, psychologic distress was associated with a higher number of patient-reported systems (Slope estimate = 2.98, $p < 0.01$) and shorter time since EOT (-0.45, $p = 0.03$). PTS was associated with a higher number of patient-reported system (1.46-fold, $p < 0.01$). Multivariable regression analyses in parent data showed parent-reported psychologic distress of patient was associated with a higher number of patient-reported systems (6.01, $p = 0.03$). Positive correlations were seen between parent-reported psychologic distress of patient and patient self-reported psychologic distress ($R = 0.58$, $p < 0.01$) and also with patient self-reported PTS ($R = 0.51$, $p < 0.01$). Parent reported psychologic distress of patient was positively correlated with parent self-reported anxiety ($R = 0.45$, $p = 0.01$) and also with parent self-reported PTS ($R = 0.42$, $p = 0.02$). **Conclusions:** A meaningful minority of survivors and parents face psychologic distress and PTS. A larger study is ongoing to expand upon our preliminary findings and examine the trajectory of psychologic distress and PTS in survivorship. Research Sponsor: NIH/NIGMS; T32GM108554.

10057 Poster Session

Longitudinal associations between chronic health condition burden and financial hardship among adult survivors of childhood cancer: A report from the Childhood Cancer Survivor study (CCSS).

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Background: Childhood cancer survivors experience a large burden of chronic health conditions (CHCs) with the progression of these conditions facilitating potential economic burden. This study examined the association between CHC progression and financial hardship in adult survivors of childhood cancer. **Methods:** The study included CCSS participants diagnosed with pediatric cancer (1970–1999) who survived > 5 years post-diagnosis and were ≥26 years old at the assessment of financial burden. Participants completed surveys (2017-2019) assessing three financial hardship domains: behavioral, material, and psychological. CHCs were self-reported at baseline and on up to 4 follow-ups. CHC severity was graded using CTCAE v4.03. To estimate the impact of multiple CHCs, a severity score was calculated based on published methods (PMID: 17595271) accounting for the frequency and grade of conditions. Notable CHC burden was defined as any CHC above low severity grade. Multivariable logistic regression evaluated associations of CHC burden with financial hardship adjusting for age at diagnosis, attained age, sex, insurance, personal income, education, marital status, smoking status, and body mass index. Additional analyses examined whether neighborhood deprivation using the Area Deprivation Index (ADI) (range 0-100) modified the relationship between CHC burden and financial hardship. **Results:** Among 3,638 evaluable participants, the prevalence of notable CHC burden was 66%, material hardship 16%, psychological hardship 26%, and behavioral hardship 21%. Survivors with very high CHC burden had 2.6-fold (95%CI 1.6-4.1) higher odds of material and 1.6-fold (95%CI 1.0-2.4) higher odds of psychological hardship vs. those with low CHC burden. Survivors who progressed to moderate, high, or very high CHC burden had 1.7-fold (95%CI 1.2-2.5) higher odds of material hardship and 1.6-fold (95%CI 1.1-2.2) higher odds of psychological hardship vs. those with persistent low CHC burden. For survivors living in more deprived neighborhoods (ADI≥50), having notable CHC burden was associated with 2.5-fold (95%CI 1.5-4.3) higher odds of material hardship vs. those without notable CHC burden. For survivors living in less deprived neighborhoods (ADI < 50), having notable CHC burden was associated with 1.5-fold (95%CI 1.1-2.2) higher odds of psychological hardship and 1.6-fold (95%CI 1.1-2.1) higher odds of behavioral hardship vs. those without notable CHC burden. **Conclusions:** Longitudinal CHC burden shows strong temporal associations with material and psychological financial hardship. Neighborhood deprivation is associated with financial hardship, beyond individual sociodemographic factors. Multi-level interventions will be crucial to address financial hardship in survivors who develop CHCs earlier than peers. Research Sponsor: National Cancer Institute; U24 CA055727.

10058 Poster Session

Treatment and lifestyle profiles of healthy aging survivors: A report from the Childhood Cancer Survivor Study.

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Background: Survivors of childhood cancer are at elevated risk for adverse health outcomes, but many maintain excellent health throughout adulthood. We sought to characterize the trajectories of, and examine factors associated with, healthy aging across the lifespan. **Methods:** We longitudinally surveyed ≥5 y cancer survivors (18-64 y) and sibling controls enrolled in the Childhood Cancer Survivor Study. "Healthy aging" was defined by 1) having a cumulative number of severe or life-threatening (i.e., grade 3+) chronic health conditions (CHCs) less than or equal to the mean of same age, same sex sibling controls; and 2) having no functional impairment or activity limitations. We then examined prevalences of healthy aging and its 2 component domains across survivor age groups (< 30, 30-39, 40-49, ≥50 y). Multivariable logistic regression models adjusted for demographic, treatment, and lifestyle factors at cohort entry estimated risk factors for healthy aging among survivors. **Results:** We analyzed 17,263 survivors (median age 39 y, IQR 32-46) and 3,378 siblings. Among all sibling age/sex groups, mean grade 3+ CHC counts were < 1. Of survivors, 53.4% (95% CI 52.7-54.2) had no Grade 3+ CHC, and 71.4% (95% CI 70.7-72.1) reported no functional impairment. Overall, 45.0% (95% CI 44.2-45.7) of survivors met criteria for healthy aging, but this prevalence decreased with age (Table). In multivariable analysis, treatment factors associated with lower odds of healthy aging included anthracycline dose (≥250 mg/m^2 vs none: OR 0.60, 95% CI 0.52-0.69), alkylator dose (≥8 g/m^2 vs none: OR 0.76, 95% CI 0.67-0.86), and stem cell transplant (OR 0.60, 95% CI 0.41-0.89). High doses of radiation to any site were also associated with less healthy aging (e.g., ≥30 Gy to brain vs none: OR 0.22, 95% CI 0.19-0.26). Baseline physical activity > 180 min/week was associated with healthy aging (vs < 180 min: OR 1.23, 95% CI 1.11-1.37). Underweight, overweight, and obese baseline BMIs had lower odds of healthy aging compared with normal BMI (ORs 0.54 to 0.82, each $p < 0.05$). Survivors treated in more recent decades were more likely to experience healthy aging (1990s vs 1970s: OR 1.26, 95% CI 1.06-1.50) even after adjusting for attained age. **Conclusions:** Among childhood cancer survivors, the prevalence of healthy aging declines with age but has improved in more recent treatment eras. Higher levels of exercise and normal BMI at baseline were associated with subsequent healthy aging, suggesting that the trajectory of aging could be improved through targeted interventions. Research Sponsor: National Cancer Institute; CA55727; National Cancer Institute; CA21765.

Prevalence (%) of outcomes across survivor age groups (95% CI).

	<30 y	30-39 y	40-49 y	≥50 y
CHC count ≤ sibling mean for age/sex	67.4 (65.8, 69.0)	59.3 (58.1, 60.5)	47.5 (46.2-48.9)	34.4 (32.6-36.2)
No functional impairment	76.0 (74.6, 77.5)	73.9 (72.8, 74.9)	69.4 (68.2-70.7)	64.1 (62.3-65.9)
Healthy aging	58.0 (56.3, 59.7)	50.8 (49.5, 52.0)	39.2 (37.8-40.5)	27.2 (25.5-28.9)

10059 Poster Session

US population-level costs and cost-savings associated with long-term follow-up (LTFU) screening for survivors of childhood cancer.

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Background: Children's Oncology Group's (COG) LTFU Guideline adherence is poor. We evaluated the impact of universal payer coverage on patient costs associated with adherence to COG-directed cardiomyopathy (CM), breast (BC), and colorectal cancer (CRC) screening. **Methods:** We reviewed coverage guidelines for Medicare, Medicaid, and commercial plans for COG screening for exposure-based CM (echocardiogram [echo] every 2-5 yrs based on cumulative chest radiation (RT) and anthracyclines), BC (yearly mammography [MAM] and magnetic resonance imaging [MRI] beginning at age 25 or 8 yrs from chest RT), and CRC (colonoscopy [COL] every 5 yrs or multitarget stool DNA [MTSD] every 3 yrs, starting 5 yrs from abdominopelvic RT or age 30). The eligible US population was estimated from SEER and American Cancer Society cancer survival rates. Cost of screening was derived from the Center for Medicare & Medicaid Services (CMS) and of lifetime treatment from published data. Net costs vs. benefits (in US $) were calculated, assuming 100% adherence, as the sum of cost-savings (i.e., treatment costs averted) and monetary value of quality-adjusted life-yrs (QALYs) gained minus costs (e.g., screening, false positives). **Results:** Screening coverage varied by payer (Table). BC screening for all US survivors with prior chest RT (n = 42,847) yielded a net benefit ranging from $0.5 to $3.4 billion, with patients paying 19.3% of costs. Among 138,702 survivors at-risk of CRC, net benefit from COL and MTSD was $5.7 and 5.0 billion. Patients nationally bore 0% of MTSD but 60% of COL costs. Among 218,322 at-risk of CM, costs exceeded cost-savings by $1.7 billion when using the median echo cost by payer but yielded a $400 million benefit when using the average cost of CMS and the lowest commercial plan. Patients bore 90% of CM costs. **Conclusions:** Screening for CM, BC, and CRC per the COG guidelines results in substantial cost savings and benefits. However, as adherence is < 100% due to copay, inadequate coverage, and low provider awareness, interventions and policies focused on boosting adherence could yield cost savings to the health system and reduce disease burden in this population. Research Sponsor: None.

		By Payer (Subset)			Cost Bearer, % (Aggregated across Payers)		Value of Cases Averted	Value of QALYs Gained	Total Cost	Net Costs (-) or Benefit (+)
COG Screening		Medicare	Medicaid	Commercial	Patient (Pt)	Payer	Billion US $, Range			
BC MAM & MRI	**Coverage**	Full, at physician's discretion	**MAM:** Full **MRI:** None	Full	19.3	80.7	NA*	2.6 - 5.9	2.1 - 2.5	0.5 - 3.4
	Pt Cost	20% copay after Part B deductible	20% copay	**MAM:** 0% **MRI:** 15-30% copay after deductible						
CRC COL or MTSD	**Coverage**	**COL:** None **MTSD:** Full	None Full	None Full	**COL:** 60	40	3.7	4.4	2.4	5.7
	Pt Cost	**COL:** 100% **MTSD:** 0%	100% 0%	100% 0%	**MTSD:** 0	100	2.9	4.0	1.9	5.0
CM Echo	**Coverage**	None	None	≤2 covered after age 18	90.3	9.7	0.01	0.74	0.36 - 2.5	-1.7 - 0.4
	Pt Cost	100%	100%	15%-30% copay after deductible						

*Not available in published models.

10060 Poster Session

Food insecurity, dietary quality, and cardiovascular risk in early childhood cancer survivors.

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Background: Childhood cancer survivors (CCS) experience cardiovascular (CV) mortality 7 times higher than the general population. Low-income and Black CCS experience significantly higher all-cause and CV mortality than peers. Food insecurity, a modifiable CV risk factor associated with lower dietary quality, has not been investigated as a potential driver of adverse CCS CV outcomes. We characterized and assessed associations between food insecurity, dietary quality, and CV risk conditions in a prospective cohort of early CCS. **Methods:** Children $<$ 18 years with a hematologic, solid, or central nervous system malignancy $<$ 12 months from completion of cancer-directed therapy were recruited at a quaternary academic pediatric cancer center. Parents/guardians completed a single-timepoint survey including validated measures of food insecurity and dietary quality. Clinical CV risk (systolic or diastolic blood pressure $\geq 95^{th}$ percentile, body mass index $\geq 85^{th}$ percentile, dyslipidemia, or impaired glucose tolerance) and therapeutic CV risk (receipt of anthracycline, chest radiation, or total body irradiation) was abstracted from the medical record. Descriptive statistics summarized dietary quality and prevalence of food insecurity. A t-test compared associations between food security status and dietary quality, followed by multivariable linear regression adjusted for age, sex, race/ethnicity, income, and diagnosis type. Logistic regression compared associations between food security status and presence of clinical CV risk conditions. **Results:** Of 135 eligible participants, 119 (88%) consented to participation and 115 (97%) completed surveys, with no missing food security or dietary data. Participants were a mean age 6.5 years and mean 4.8 months from end of therapy. Twenty-seven percent (n = 31, 95% CI: 19-36%) of participants lived in food-insecure households. Mean child dietary quality was 27.6 (SD 5.3) on a 52-point scale (higher scores reflect higher quality, US adult mean score 35.0). Dietary quality was significantly lower for participants in food-insecure households compared to food-secure households on univariate analysis (25.9 vs 28.2, p = 0.04); in multivariable analyses, this difference was no longer significant. Among the subcohort (n = 97) consented to medical record abstraction, 84% (n = 81) had a CV risk factor (47% [n = 38] clinical conditions, 26% [n = 21] therapeutic exposures, and 27% [n = 22] both). Frequency of clinical CV risk conditions did not differ between children with and without food insecurity (58% vs 63%, p = 0.61). **Conclusions:** One in four children in early cancer survivorship lives with food insecurity. These children concurrently experience multiple CV risk factors and suboptimal dietary quality. Interventions targeting food insecurity and other modifiable CV risk factors are urgently needed to mitigate CV late effects and advance equity in survivorship outcomes. Research Sponsor: Conquer Cancer, the ASCO Foundation; St. Baldrick's Foundation.

10061 Poster Session

Risk assessment and development of a machine learning–based prediction model for survival in patients with medulloblastoma.

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Background: While clinical risk factors have long guided medulloblastoma (MB) treatment, the significance of genetic events in therapeutic strategies has not been fully elucidated. We aimed to explore whether molecular risk categories could inform management by analyzing long-term follow-up profiles, and concurrently to establish and validate an explainable prediction model for MB based on machine learning (ML) approaches, and to assess its prognostic implications in patients. **Methods:** A multicenter cohort of 729 patients from 2001 to 2023 was enrolled as a discovery cohort. Data from 511 patients from international MB consortia were used to validate. Multivariate survival analyses assessed the associations between radiotherapy dose and survival by different molecular risk stratifications which integrated clinical and genetic events, followed by training and internal and external validation of models. The area under the receiver-operating-characteristic curve (AUROC) and decision curve analysis (DCA) were used to compare the predictive performance of six ML models. The SHapley Additive exPlanation method was used to explain the final model. **Results:** Fifteen-year OS and DFS rates were 64.1% (95% CI, 57.9%-71.0%) and 59.1% (95% CI, 53.2%-65.5%) for clinical average-risk group (n = 554), and 55.9% (95% CI, 44.4%-70.2%) and 60.6% (95% CI, 51.9%-70.7%) for clinical high-risk group (n = 175), respectively. Within the high-risk stratification of SHH-MB, higher posterior fossa tumor bed (PFTB) total dose ($\geq$ 55.8 Gy) combined with reduced craniospinal irradiation (CSI) dose (23.4 ~ $<$ 30.6 Gy) was associated with better prognosis. In Gr.3-MB, MYC amplification (activation), as a high-risk marker of dissemination, indicated that CSI dose should be escalated to high intensity (36.0 Gy, p = 0.03) for survival benefits. In the model of Gr.4-MB, CDK6 activation well stratified patients, with 10-year OS of 71.0% (95% CI, 54.0%-93.5%) for average-risk and 52.1% (95% CI, 39.5%-68.8%) for high-risk group. The XGBoost method demonstrated the most optimal predictive efficacy among the six ML models, as evidenced by the training set AUROC of 0.75 (95% CI 0.70-0.80) for 5-year survival rates, 0.75 (0.69-0.80) for 10-year survival rates, and 0.80 (0.72-0.87) for 15-year survival rates in all patients. The final model could accurately predict survival rates in both internal and external validations, and has been deployed through a free, publicly available online software interface. **Conclusions:** The molecular risk stratification was suggested to potentially guide risk-adapted radiotherapy. Except that 36.0 Gy CSI dose is warranted for Gr.3-MB with MYC amplification, CSI reduction is recommended. Furthermore, this study, based on clinical and molecular information, constructs an available survival prediction tool for MB patients. Research Sponsor: National Natural Science Foundation of China; 82273343; Capital Medical Fund for Excellent Young Scholars; KCB2304.

10062 Poster Session

Retinoblastoma patient outcomes in the contemporary era: The RIVERBOAT Consortium.

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Background: Retinoblastoma (RB) is the most common childhood eye tumor. Intraocular RB cure rates approach 100%. Therefore, treatment now focuses on globe salvage and preserving functional vision. The Research into Visual Endpoints and RB Health Outcomes After Treatment (RIVERBOAT) consortium was established to examine patient outcomes in the transitional era from systemic to intraocular therapy. **Methods:** Patients with RB treated at 13 North American centers from 2008-2022 were identified. Medical record abstraction was performed for disease presentation, visual acuity, treatment, globe salvage and functional outcome. Enrollment on the study included submission of retrospective data and prospective data on newly diagnosed patients as well as retrospective data from chart reviews. **Results:** 830 patients (68% white race, 77% non-Hispanic ethnicity) were enrolled. In 420 of these, data was limited to chart review. Median age at diagnosis of the 830 patients (1165 eyes) was 1 year (0 - 16.3) and at enrollment was 7.8 years (0 - 28.6). 60% had unilateral disease and the eye group distribution (International Intraocular Retinoblastoma Classification) was 10% A, 16% B, 12% C, 31% D, 27% E, and 4% unknown (UK). Of the 1165 affected eyes, major treatment modalities included primary enucleation (15%), systemic chemotherapy (SC) (36%), intraarterial chemotherapy (IAC) (10%), SC followed by IAC in 9%, and intravitreal chemotherapy in combination in 6%. SC only was used in 55-59% of those with A-C eyes compared to 29% of D eyes. IAC only was used in 20% of D eyes and 16% of C eyes. Secondary enucleation occurred in 151 eyes (14%): 63/416 (15%) of SC; 34/120 (28%) of IAC; 25/106 (24%) of SC followed by IAC; 29/523 (6%) other treatments. The overall globe salvage rate was 86%. Second malignancies occurred in 5, metastatic disease in 8 and pineoblastoma in 3 patients. Eleven patients died of RB (1%). Visual acuity after treatment was reported in 229 eyes: 106 (eye group 24 A, 37 B, 22 C, 19 D, 3 E, 1 UK) had normal vision (20/20-20/40). 38 eyes, (6 A, 11 B, 4 C, 10 D, 5 E, 2 UK) had moderate vision loss ($>$ 20/40 – 20/70). Twenty-five eyes (5 B, 2 C, 16 D, 2 E) had low vision ($>$ 20/70 $<$ 20/200), and 60 eyes (12 B, 7 C, 32 D, 8 E, 1 UK) were legally blind ($>$20/200). In those treated with IAC only, normal vision was found in 30% of eyes, moderate vision loss in 22%, low vision in 13%, and legal blindness in 35%. In those treated with SC only, normal vision was noted in 53% of eyes, moderate vision loss in 11%, low vision in 11%, and legal blindness in 25%. In those treated with SC followed by IAC, normal vision was reported in 32%, moderate vision in 26%, low vision in 5% and legal blindness in 37%. **Conclusions:** We demonstrate the significant benefits witnessed by the evolution of RB therapy. Cure rates remain high, with a very low incidence of second malignancies, metastatic disease or trilateral RB. Eye salvage rate was excellent, avoiding low vision or legal blindness in two-thirds of the patients. Research Sponsor: None.

10063 Poster Session

Genome-wide association study of neurocognitive outcomes among childhood cancer survivors.

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Background: Long-term survivors of childhood cancer experience heightened risk of late effects, with about 40% developing cognitive impairment. Established risk factors include cranial radiation and specific chemotherapies. Variability in treatment-related outcomes has been associated with genetic factors, though prior studies examined targeted pathways and not whole genome approaches. **Methods:** Participants included 4,077 childhood cancer survivors with whole genome sequencing and direct neurocognitive testing from the St. Jude Lifetime Cohort Study (SJLIFE). The mean (standard deviation) age at primary cancer diagnosis was 7.8 (5.7) years, and 28.5 (10.3) years at neurocognitive testing; 52.3% were male; 78.9% were Non-Hispanic White. Linear regression evaluated associations between common genetic variants (minor allele frequency, MAF≥1%) and 20 neurocognitive measures (as age-adjusted Z-scores). Analyses were adjusted for sex, age at primary childhood cancer diagnosis, age at neurocognitive testing, cumulative doses of high-dose methotrexate, intrathecal methotrexate, anthracyclines and cranial radiation, and genetic ancestry . Loci with $P \leq 5x10^{-8}$ were considered genome-wide significant and evaluated in stratified analysis by genetic ancestry and treatment exposures. **Results:** 21 SNPs met genome-wide significance for associations with ≥1 neurocognitive measure, 9 SNPs with a MAF ≥1% in EUR (n = 3,312) and AFR (n = 636) survivors. All 9 SNPs had 1.1-3.6 times larger effect sizes in AFR compared to EUR. The biggest differences in ancestry groups were seen when stratifying analyses by anthracycline exposure. An intronic variant in *ERG*, rs1309269486, had a 2.0-times larger effect on motor speed in exposed EUR ($\beta = -0.70$; $P = 2.9x10^{-6}$) compared to unexposed EUR ($\beta = -0.35$; $P = 0.039$). In AFR, rs1309269486 was only associated with motor speed in unexposed survivors ($\beta = -1.33$; $P = 2.9x10^{-3}$), with a 3.8-times greater effect size compared to unexposed EUR. *ERG* has been shown to play a role in neurogenesis. Another intronic variant in *P2RY12*, rs1755678683, also showed a 1.8-times larger effect on attention span in exposed EUR ($\beta = -0.68$; $P = 5.9x10^{-4}$) than unexposed EUR ($\beta = -0.38$; $P = 0.035$). However, it was associated with attention span in only unexposed AFR ($\beta = -1.28$; $P = 2.1x10^{-3}$), showing 3.4-times greater effect than in unexposed EUR. *P2RY12* plays a role in microglia function, neuroinflammation, and neurodegeneration. An intronic variant in *COL15A1*, rs1837227843, was associated with working memory in exposed EUR ($\beta = -0.47$; $P = 5.3x10^{-7}$) and unexposed AFR ($\beta = -0.58$; $P = 4.9x10^{-3}$). While *COL15A1* is highly expressed in many brain tissues, previous associations with neurocognition have not been established. **Conclusions:** These findings highlight the independent and combined role (with treatment) of genetics and genetic ancestry in adverse neurocognitive impairment among survivors of childhood cancer. Research Sponsor: National Cancer Institute; National Cancer Institute; the American Lebanese Syrian Associated Charities.

10064 Poster Session

Accelerated aging among long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS).

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Background: Cross-sectional studies have suggested childhood cancer survivors demonstrate a pattern of functional limitations and morbidity consistent with premature aging, but cannot confirm if aging is accelerated relative to peers without cancer. We used longitudinal data to characterize aging using a Deficit Accumulation Index (DAI) which examines the accumulation of multiple aging-related deficits. **Methods:** We included 5+ year survivors of childhood cancer (N=21,856; at entry mean age 26.7 [SD 6.1], 18.7 [4.7] years post diagnosis) and siblings (N=4,628, mean age 29.1 [7.1]) from the CCSS, a longitudinal prospective cohort study. Participants completed questionnaires at up to four timepoints (mean[SD] follow-up 9.5 [8.9] years), with DAI scores generated as the proportion of deficits out of 30 items related to aging, including chronic conditions (e.g. hearing loss, hypertension), psychosocial and physical function, and activities of daily living. The total score range is 0 to 1; and a moderate clinically meaningful difference is 0.02. As survivors completed multiple surveys at varying intervals, attained age was used as the time scale. Linear mixed models compared DAI in survivors to siblings with an attained age*survivor interaction term to determine if DAI was increasing faster in survivors, adjusted for the first DAI score, age at first DAI and sex. Similar models examined DAI changes associated with treatments among survivors. **Results:** The overall adjusted mean [95%CI] DAI was 0.195[0.194, 0.196] for survivors and 0.179 [0.177,0.180] for siblings ($p<0.001$). Survivors experienced more rapid increase in DAI over time compared to siblings ($p<0.001$). For example, at age 20 there was no difference in DAI between survivors and siblings, however the mean difference [95%CI] in DAI between survivors and siblings steadily increased with age to 0.011[0.009, 0.013] at 30 years, 0.024[0.022, 0.026] at 40 years, and 0.038[0.035, 0.040] at 50 years; p's<0.001 (Table). Survivors who received abdominal, cranial or chest radiation experienced more rapid increase in DAI over time compared to those who did not (p's<0.001). Survivors who received platinum agents or neurosurgery also experienced a more rapid increase in DAI over time (p's<0.001). **Conclusions:** Our data confirm survivors of childhood cancer experience significant age acceleration relative to peers. Given the ease of measuring DAI using self-reported data, this tool may be used to routinely monitor survivors and identify those at risk for adverse aging-related outcomes so that we may intervene and mitigate their accelerated aging trajectory. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U24CA55727; National Cancer Institute/U.S. National Institutes of Health; R00256356.

Mean difference in DAI in survivors vs. siblings.

	Mean difference (95% CI)	P-value
Age at DAI		
20	-0.003(-0.006, 0.000)	0.0541
30	0.011(0.009, 0.013)	<.0001
40	0.024(0.022, 0.026)	<.0001
50	0.038(0.035, 0.040)	<.0001
60	0.051(0.047, 0.055)	<.0001
70	0.064(0.059, 0.070)	<.0001

Cardiovascular risk factor control and risk of future cardiovascular events in survivors of childhood cancer: A report from the St. Jude Lifetime cohort.

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Background: Modifiable cardiovascular risk factors (CVRFs; hypertension, diabetes, dyslipidemia) contribute to the excess health-related death in long-term survivors of childhood cancer. However, whether control of CVRFs reduces the risk of major adverse cardiovascular events (MACE) in survivors is not known. **Methods:** Prevalence of hypertension (HTN), diabetes (DM) and LDL cholesterol elevation (LDL) was assessed via in-person assessments in 5+ year survivors ≥18 years old in the St. Jude Lifetime Cohort. Based on ACC/AHA primary prevention guideline recommendations, sub-optimal CVRF control was defined as blood pressure ≥140/90 mmHg, hemoglobin A1c ≥7.0%, and LDL ≥130 mg/dl. MACE was defined as new onset cardiomyopathy, myocardial infarction, stroke and/or cardiovascular death. Piecewise exponential models estimated the multivariable adjusted relative risk (RR) with 95% confidence intervals (CI) for MACE among survivors according to degree of CVRF control. Models were adjusted for sociodemographic factors, physical activity, smoking status, chronic kidney disease, and cancer treatment exposures (anthracycline chemotherapy, chest and/or brain irradiation). **Results:** Among 4876 adult survivors of childhood cancer, 36.1% had HTN, 8.4% DM and 56.5% elevated LDL at first assessment (mean age 28.6 years, standard deviation 9.1). One-third of survivors (33.5%) had at least one sub-optimally controlled CVRF. Among those with HTN, DM or LDL, 30%, 33% and 52% were sub-optimally controlled, respectively. In multivariable models, sub-optimal LDL control was associated with a > 8-fold higher risk of MACE compared to those with no LDL elevation (RR 8.4, CI 4.2 – 19.3; Table). This was more than twice the risk observed in those with well-controlled LDL compared to no LDL elevation (RR 4.0, CI 1.9 – 9.4; p-value <0.001). Similarly, sub-optimal DM control vs never having DM was associated with increased MACE risk (RR 3.4, CI 1.8 – 6.1) with twice the risk in those with sub-optimal control compared to well-controlled DM (p = 0.05; RR well-controlled DM vs no DM 1.6, CI 0.9 – 2.8). HTN, compared to no HTN, was associated with a 3 to 4-fold increase in risk of subsequent MACE, regardless of degree of control. **Conclusions:** Survivors of childhood cancer had a high prevalence of sub-optimally controlled CVRFs that was associated with an increased MACE risk. Optimal control of CVRFs among adult survivors of childhood cancer may reduce the risk of MACE. These findings motivate an intervention trial in intensive CVRF control. Research Sponsor: U.S. National Cancer Institute; U01 CA195547; U.S. National Cancer Institute; P30 CA21765; American Lebanese-Syrian Associated Charities (ALSAC).

CVRF Control	RR of MACE (95% CI)	P-value comparing RR
LDL elevation		
Sub-optimal LDL vs no LDL elevation	**8.4 (4.2 – 19.3)**	**<0.001**
Controlled LDL vs no LDL elevation	**4.0 (1.9 – 9.4)**	
Diabetes		
Sub-optimal DM vs no DM	**3.4 (1.8 – 6.1)**	**0.05**
Controlled DM vs no DM	1.6 (0.9 – 2.8)	
Hypertension		
Sub-optimal HTN vs no HTN	**3.9 (2.2 – 7.0)**	0.28
Controlled HTN vs no HTN	**3.0 (1.9 – 4.8)**	

10066 Poster Session

Breast cancer recurrence and mortality among survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS).

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Background: Survivors of childhood cancer are at high risk for developing subsequent breast cancer (BC). However, BC recurrence risk and survival after BC recurrence has not been evaluated in survivors of childhood cancer. **Methods:** Analyses included female 5-year survivors participating in CCSS with pathology-ascertained breast carcinomas (in situ or invasive) diagnosed from 1981-2016 at age ≥18y. BC treatment was evaluated against chronological period-specific National Comprehensive Cancer Network guidelines for primary BC. Recurrent BC cumulative incidence was estimated treating death as a competing risk among survivors and females with first primary BC (controls) matched one-to-one by demographics and first BC clinical characteristics including diagnosis age/year, histology and race/ethnicity (206 pairs with complete data). Among survivors and controls with recurrent BC, all-cause mortality was evaluated with cumulative incidence with time at risk starting at relapse and hazard ratios from multivariable Cox regression models adjusted for age and calendar year of recurrence and race/ethnicity. **Results:** Among the 431 childhood cancer survivors with subsequent BC (median diagnosis age: 40 years, IQR: 35-44), 68 developed recurrent BC. Compared with matched controls, survivors had similar 10-year BC recurrence risk (survivors: 14%, 95% CI: 9-20% versus controls: 12%, 95% CI: 9-18%; P=0.52). Among survivors with BC recurrence, Hodgkin lymphoma was the predominant primary cancer diagnosis (63%) and first subsequent BCs were largely early stage (stage 0: 8%; stage I/II: 69%) and estrogen (71%) or progesterone (80%) receptor positive. Most (84%) received first BC treatment following national guidelines for primary BC. However, nearly half (47%) underwent bilateral mastectomies (81% occurring before recurrence) and most received chest radiotherapy (86%) or anthracycline chemotherapy (69%) for either their primary childhood cancer or first subsequent BC. A total of 48 survivors died after BC recurrence, mostly related to BC (83%) or cardiovascular causes (11%). Following recurrence, the 10-year overall mortality probability was significantly higher among survivors (89%, 95% CI: 61-97%) than controls (42%, 95% CI: 18-58%; P=0.0025) and survivors had an adjusted 2.6-fold (95% CI: 1.05-6.49) greater risk of death. **Conclusions:** Although the risk for BC recurrence among childhood cancer survivors with subsequent BC is similar to females with primary BC, this vulnerable population faces substantially greater mortality risk after recurrence. Future studies to identify early predictors of subsequent BC and BC recurrence among survivors are needed to reduce mortality risk. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; K08 CA234232, LM Turcotte, principal investigator; U24 CA55727, GT Armstrong, principal investigator.

10068 Poster Session

Financial hardship and non-adherence to lifestyle and surveillance recommendations in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS).

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Background: The association between different aspects of medical financial hardship and non-adherence to healthy lifestyle recommendations and surveillance for subsequent neoplasms (SN) and cardiomyopathy in long-term survivors of childhood cancer is unknown. **Methods:** A randomly selected subset of participants in the CCSS completed a financial hardship survey and a follow-up survey assessing lifestyle behaviors and adherence to recommended surveillance. Presence of financial hardship was determined by affirmative response to ≥1 item in material (e.g., high out-of-pocket costs), behavioral (e.g., delaying care due to cost), or psychological (e.g., worry about financial situation) hardship domains. Outcomes included "not meeting physical activity guidelines" (< 9 metabolic-equivalent-of-task-hour/week moderate to vigorous activity), "problematic drinking" (> 7 drinks/week or > 3 drinks/day [women], > 14 drinks/week or > 4 drinks/day [men]), current smoker, unhealthy BMI (< 18.5 or ≥30 kg/m^2), and non-adherence to surveillance for breast, colorectal, and/or skin cancer, and cardiomyopathy screening according to the Children's Oncology Group guidelines. Logistic regression models, adjusted for age at the most recent survey, sex, race/ethnicity, education, and chronic health conditions, examined the association of material, behavioral, and psychological hardship with healthy lifestyle and surveillance outcomes. **Results:** A total of 3,322 survivors, at a median of 34.4 (range:19.7-51.4) years from diagnosis and 41 (20-69) years of age at the most recent survey were included. Presence of material hardship alone was associated with higher risk of not meeting physical activity guidelines (odds ratio 1.6, 95%CI 1.2-2.1) and unhealthy BMI (1.4, 1.1-1.8). Presence of both material and behavioral (1.8, 1.2-2.6) or material and psychological (1.8, 1.4-2.4) hardships further increased the risk for unhealthy BMI. Presence of all 3 hardship domains was associated with higher risk of unhealthy BMI (2.2, 1.8-2.7). Behavioral hardship (2.2, 1.1-4.6) and psychological hardship (3.9, 2.4-6.4) alone were associated with higher risk of being a current smoker at time of follow-up, with presence of both further increasing the risk for smoking (4.1, 2.3-7.3). Presence of psychological hardship alone was associated with higher non-adherence to cardiomyopathy screening (1.3, 1.0-1.8) among those at high risk. Associations between hardship and SN surveillance were not significant. **Conclusions:** Financial hardship is associated with non-adherence to healthy lifestyle and recommended screening for cardiomyopathy among adult survivors of childhood cancer. Findings underscore the need for strategies to identify and mitigate financial hardship and improve adherence to recommended lifestyle and surveillance. Research Sponsor: National Cancer Institute; U24 CA55727.

Assessment of smartwatch-based electrocardiogram (ECG) abnormality detection among childhood cancer survivors.

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Background: Childhood cancer survivors (CCS), exposed to cardiotoxic cancer therapies, are at lifelong risk for premature cardiovascular disease. However, adherence to guideline recommended screening is low later in life, long after cancer treatment. Novel wearable technologies offer a potential low-cost, easy screening method for arrythmias in CCS, including AF, bradycardia, and tachycardia. However, their utility in population level screening for CCS is unknown. **Methods:** We collected paired single lead smartwatch with FDA cleared ECG functionality and 12-lead 10 second ECGs from adult participants in the St. Jude Lifetime Cohort Study (SJLIFE) who were treated for their primary cancer 1962-2012 and survived ≥5 years. Participants completed an in-person comprehensive examination including a standard 10 second 12-lead ECG recording as well as single lead rhythms were collected using a smartwatch. The smartwatch provided automated annotations including sinus rhythm, AF, bradycardia (HR<60 bpm), tachycardia (HR>100 bpm), and inconclusive rhythm. We compared the smartwatch generated statements to reference diagnostic statements generated by GE MUSE system. **Results:** There were 598 same day ECG pairs in 580 participants (83% White, 14% Black, 50% male, and mean age(SD) 37(10) years). The mean(SD) times between smartwatch and reference ECG recordings were 32(50) minutes. The heart rate from reference ECG and smartwatch ECG had a Pearson Correlation of r=0.85 (p<0.001). The smartwatch ECGs presented statistically significantly (p<0.001) higher heart rates compared to reference ECGs with mean heart rate difference (95% confidence interval) of 1.2 (0.5-1.8) beats per minute. Standard 12-lead ECGs processed by GE MUSE annotations included 478 (80%) sinus rhythm and 120 (20%) as 'no sinus rhythm' with 1 (0.2%) AF, 57 (9.5%) sinus bradycardia, 18 (3.2%) sinus tachycardia and 28 (6.4%) other rhythms. The smartwatch assigned sinus rhythm to 590 (98.7%) of these ECGs. The detailed rhythm annotations between reference ECG and smartwatch ECGs are summarized in Table 1. The smartwatch detected only 3.5% (2 of 57) of reference bradycardia, none of the 18 reference tachycardia and 1 AF event. Overall, among 120 ECGs labelled as 'no sinus rhythm' by the reference device, only 3 (2.6%) of them were also labeled as 'no sinus rhythm' by the smartwatch. **Conclusions:** The smartwatch considered in this study produces heart rate that is not clinically different than heart rate calculated by a reference 12-lead ECG. However, the ECG abnormalities identified by reference ECGs were typically missed by the smartwatch. Research Sponsor: National Cancer Institute; R01CA261834.

Comparison of GE MUSE and smartwatch ECG statements.

		Smartwatch Statements					
		Sinus Rhythm	Atrial Fibrillation	Low Heart Rate	High Heart Rate	Inconclusive/ Poor	
GE MUSE Statements	Sinus Rhythm	478	0	3	0	2	483
	Atrial Fibrillation	1	0	0	0	0	1
	Bradycardia	55	0	2	0	0	57
	Tachicardia	18	0	0	0	1	19
	Other Rhythm	38	0	0	0	0	38
	Total	590	0	6	0	3	598

Predicting valvular heart disease in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime Cohort (SJLIFE).

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Background: Radiotherapy (RT)-related valvular heart disease (VHD) is an understudied late toxicity of childhood cancer therapy. We aimed to define the risk of VHD with clinical data available at 5 and 20 years from cancer diagnosis. **Methods:** Mean heart RT doses were estimated for participants of the CCSS and SJLIFE cohorts treated with RT. Two piecewise exponential regression prediction models were developed in the CCSS, from entry into survivorship (5 years post cancer diagnosis) and 20 years post diagnosis (inclusive of age- and lifestyle-acquired risk factors), to assess subsequent risk of developing severe/life-threatening/fatal VHD (≥ grade 3 Common Terminology Criteria for Adverse Events [CTCAE]) by age 50 years. Models were validated among clinically assessed SJLIFE survivors. **Results:** Among 18,807 CCSS participants [mean age (±standard deviation) at diagnosis = 8.1 (5.8) years and 40 (11.1) at assessment] including 9,998 treated with RT, 164 (0.9%) reported VHD after cohort entry. Of those ≥20 years post diagnosis (n = 16,618) [7.9 (5.8) years at diagnosis; 42.5 (9.6) at assessment] 138 (0.8%) reported VHD. In SJLIFE, 44 (1.0%) of 4,388 survivors, including 2,103 treated with RT, and 35 (1.4%) of 2,423 ≥20-year survivors had VHD (mean ages at diagnosis and assessment: 7.8 [5.7] and 32 [12] years; 7.6 (5.5) and 38.7 (9.2) years, respectively). Prediction performance at age 50 years was good for both models [areas under the receiver operating characteristic curves 0.84 (95% CI 0.79-0.89) and 0.87 (95% CI 0.81-0.91)]. For each 10 Gy of heart RT, the rate of VHD increased approximately 2.5-fold (Table). Acquired risk factors, except glucose intolerance, further increased the risk, marginally for hypertension, significantly ($p < 0.05$) for obesity (RR 1.7 95% CI 1.0-2.8) and dyslipidemia (RR 2.3 95% CI 1.3-4.0). **Conclusions:** In the first study to develop validated risk prediction models for VHD in survivors of childhood cancer, mean heart RT dose and acquired factors significantly increased the risk, suggesting opportunities for intervention. Research Sponsor: U.S. National Institutes of Health; R01CA261750; U.S. National Institutes of Health; U24 CA55727; U.S. National Institutes of Health; U01 CA195547; American Lebanese Syrian Associated Charities (ALSAC).

Rate ratios (RR) of VHD.

	From entry into survivorship		From 20-year post diagnosis	
	RR	(95% CI)	RR	(95% CI)
Mean heart RT dose (per 10 Gy)	2.4	(2.2-2.7)	2.5	(2.2-2.9)
Age at diagnosis (years)				
<5	referent		referent	
5-9	1.1	(0.6-2.1)	1.2	(0.6-2.5)
10-15	1.1	(0.6-2.1)	1.3	(0.6-2.6)
≥15	1.1	(0.6-2.1)	1.2	(0.6-2.6)
Female sex	1.1	(0.8-1.5)	1.3	(0.9-1.9)
Race/Ethnicity				
non-Hispanic White	referent		referent	
non-Hispanic Black	1.3	(0.5-2.8)	0.8	(0.2-2.3)
Other	1.1	(0.6-1.6)	1.0	(0.6-1.7)
Anthracycline dose (mg/m^2)				
None	referent		referent	
<100	0.6	0.1-1.6	0.8	(0.2-2.2)
100-249	0.9	0.5-1.4	0.9	(0.5-1.5)
≥250	1.5	1.0-2.2	1.3	(0.8-2.1)
Acquired risk factors*				
Glucose intolerance	N/A		0.3	(0.02-1.3)
Smoking (Y/N)			1.1	(0.8-1.5)
Hypertension			1.6	(0.9-2.7)
Obesity			1.7	(1.0-2.8)
Dyslipidemia			2.3	(1.3-4.0)

*≥grade 2 CTCAE.

10071 Poster Session

Characteristics and concomitant congenital abnormalities among newborns with cancer: A population level analysis.

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Background: Congenital cancers are rare, occurring in 223 per million infants annually. Neuroblastoma, leukemia, and CNS tumors are most common. Up to one-third of cases involve genetic predispositions, emphasizing the need to understand developmental abnormalities for improved surveillance, prognosis, and targeted therapies. **Methods:** A retrospective population-based cohort study was conducted utilizing the Texas Inpatient Public Use Data File (TIPUDF) from 2016 to 2023. The target population consisted of all hospitalizations with Newborn in the source of admission column of the TIPUDF. Hospitalizations discharged more than one year after birth were excluded from the study. The primary exposure was a diagnosis of cancer identified using International Classification of Diseases, Tenth Revisions, Clinical Modification (ICD-10-CM) codes selected from diagnosis chapter NEO: Neoplasms and beginning with C. Outcome variables were selected from diagnosis chapters MAL: Congenital Malformations, Deformations and Chromosomal Abnormalities and PNL: Certain Conditions Originating in the Perinatal Period. Continuous variables are summarized as mean and standard deviation (SD) categorical variables are summarized as counts and percentages. Fisher's exact test and t-tests assessed group differences, with the standardized mean difference (SMD) used as an effect size. **Results:** Out of the 2,906,295 newborn admissions in the TIPUDF from 2016-2023, 136 had a diagnosis of cancer. Compared to newborn admission without cancer, newborn admissions with cancer were more often male (62.5% vs 51.0%). Compared to newborns without cancer, newborns with cancer were associated with higher rates of congenital malformations, deformations and chromosomal abnormalities including atrial septal defects (38.2% vs 1.7%, SMD = 1.0256, $p < 0.0001$), anomalies of the aorta (1.6% vs 39.7%, $p < 0.0001$), undescended testicles (0.5% vs 2.9%, SMD = 0.1932, $p < 0.0037$), ventricular septal defects (15.4% vs 0.7%, SMD = 0.5647, $p < 0.0001$), Atresia and stenosis of urethra and bladder neck (2.2% vs 0.0%, SMD = 0.2119, $p < 0.0001$), Cleft lip/palate (2.2% vs 0.1%, SMD = 0.1935, $p = 0.0009$), anomalies of ureter (1.5% vs 0.0%, SMD = 0.1695, $p < 0.0003$). Newborns with cancer were more frequently affected by maternal conditions and complications including polyhydramnios (2.9% vs 0.2 %, SMD = 0.2260, $p < 0.0001$) and maternal infectious and parasitic diseases (7.4% vs 2.6%, SMD = 0.2193, $p = 0.0032$). **Conclusions:** Congenital cancers are rare but closely linked to congenital abnormalities and maternal complications, emphasizing the importance of early detection and tailored care. Future studies should explore underlying mechanisms and design effective surveillance strategies to enhance early diagnosis and outcomes. Research Sponsor: None.

10072 Poster Session

Evaluating survivorship-related communication gaps to develop a community health worker-led intervention for Hispanic/Latino young adult childhood cancer survivors and their families.

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Background: Open communication among young adult childhood cancer survivors (YA-CCS), parents, and clinicians helps YA-CCS understand their cancer history, health risks, and survivorship care needs. However, Hispanic/Latino (H/L) YA-CCS families who prefer a language other than English face significant communication barriers during clinical encounters with English speaking clinicians. As part of an ongoing study aimed at developing an intervention to facilitate family-centered communication, we report here on interviews conducted with H/L YA-CCS and their parents. **Methods:** We held small group and individual interviews in English and Spanish with H/L YA-CCS (ages 18-25, ≥5 years post-diagnosis) and separately with parents of H/L YA-CCS. Transcripts were analyzed qualitatively using thematic analysis in Dedoose software. Participants were recruited through our collaboration with a community-based organization (CBO) and in a pediatric oncology clinic. Using a structured human-centered design process, we assembled a design team of community partners to ideate and prototype an intervention. **Results:** Ten YA-CCS (5 female, 5 male; all bilingual) and 10 parents (all female; Spanish-language preferred) participated, representing 13 families. YA-CCS were median age (min-max) 20.5 (18-25) years and 9 (6-15) years post-diagnosis. YA-CCS described knowledge gaps due to being excluded from parent-clinician conversations during treatment and ongoing avoidance of cancer discussions within families due to emotional burden. Many YA-CCS and parents shared that yearly survivorship clinic visits evoke stress, nervousness, and a sense of being unprepared, often leaving them overwhelmed. Some linked hesitancy to discuss cancer or ask questions during visits to their cultural norms. Guided by these insights, we leveraged our community-clinic partnership to co-develop an intervention to facilitate family-centered communication. In 3 design workshop sessions, CBO staff designed an early prototype for a "pre- and post-visit preparation" communication intervention, in which a community health worker meets with each YA-CCS-parent dyad before and after a survivorship clinic visit to help elicit questions, clarify topics, and debrief action items. **Conclusions:** Effective triadic communication is essential to bridge gaps in cancer survivorship care among H/L YA-CCS. Listening directly to H/L YA-CCS and parents identified communication barriers that are being addressed in the development of a culturally and linguistically tailored intervention to support families affected by cancer. Interviews and the intervention design process are ongoing and updated data will be presented at the meeting. Research Sponsor: Conquer Cancer, the ASCO Foundation; National Institutes of Health, National Cancer Institute; 1K08CA285829-01.

10073 Poster Session

Development of a pediatric oncology financial toxicity outcome measure with content and face validity: The Parent-Reported Instrument of Costs and Experiences with financial toxicity (PRICE) measure.

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Background: Cancer treatment often leads to adverse financial consequences for patients and families (i.e., financial toxicity, FT). There is no validated measure to quantify FT in pediatric cancer settings, limiting research in this area. **Methods:** We applied a stepwise approach to measure development consistent with ISPOR guidelines. First, we conducted qualitative concept elicitation interviews with family caregivers of children treated for cancer, 3-24 months following diagnosis. Second, we drafted de novo survey items guided by salient domains and aspects of FT from the interviews. Items were reviewed by a multi-institutional panel of experts in oncology and/or FT-related research, who provided numeric ratings of item relevance for aggregation into content validity index (CVI) scores. Experts also provided free text feedback on clarity and content. Items with CVI < 0.75 were removed or revised by a consensus-based process. The revised item list was organized into a preliminary measure and forward and back translated into Spanish. Finally, we pretested items with a new cohort of caregivers in English and Spanish, through iterative rounds of language-concordant cognitive interviews (3-4 per round). Between each round, we reviewed and revised the survey to optimize comprehension, decision and response processes, and flow. **Results:** Concept elicitation with 21 caregivers (86% mothers, 47% college-educated, 14% in Spanish) led to the creation of 56 initial survey items across 5 domains of FT: increased household spending, diminished income, household material hardship, psychological distress related to finances, and behaviors in response to FT. The expert panel (n = 11) consisted of 5 providers, 2 clinical social workers, 2 nurse researchers, and 2 non-clinician researchers, with 6 members external to the study institution. CVI was < 0.75 for 13 items; 11 of these were removed and 2 were revised based on free text feedback. Of 43 items with CVI ≥ 0.75, 9 were removed based on feedback and/or overlap with more highly rated items. Cognitive interviews were held with 19 caregivers (15 in English, 4 in Spanish; 74% mothers, 53% college educated) over 5 iterative rounds. The 36 remaining items were revised and/or removed, and ultimately organized into 16 questions, one of which was added during this phase based on caregiver feedback. In the final round of interviews, participants reported no concerns with content, clarity, or organization in either language. **Conclusions:** We developed a novel outcome measure with content and face validity to assess FT specifically in pediatric oncology settings. Next steps consist of field testing to evaluate the measure's psychometric properties and other dimensions of validity. Potential future applications include use as a study endpoint and/or clinical screening tool. Research Sponsor: Conquer Cancer, the ASCO Foundation.

TPS10074 Poster Session

A phase 1/2, open-label study evaluating the efficacy, safety, and pharmacokinetics of luveltamab tazevibulin in infants and children < 12 years of age with *CBFA2T3::GLIS2* acute myeloid leukemia.

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Background: *CBFA2T3::GLIS2*-rearranged acute myeloid leukemia (AML) is a rare subtype of AML occurring exclusively in very young children and is associated with poor prognosis ($<15\%$ 5-year event-free survival [EFS]) with best-available multi-agent chemotherapy. Luveltamab tazevibulin (luvelta) is an anti–FRα-targeting antibody-drug conjugate with a stable cleavable linker and a 3-aminophenyl hemiasterlin warhead (DAR = 4), which induces cytotoxic and immunologic cell death. *CBFA2T3::GLIS2* AML uniquely expresses high cell surface levels of the FRα, suggesting that FRα-targeted therapies may be effective. Preclinical studies have demonstrated that treatment with luvelta can result in leukemia clearance. Preliminary safety and efficacy data from 25 children with relapsed/refractory *CBFA2T3::GLIS2* AML treated with luvelta via compassionate use are promising [Williams, et al, BLOOD 2023, 142 (1): 4295]. **Methods:** This registration-enabling phase 1/2 study (clinicaltrials.gov NCT06679582) will investigate the pharmacokinetics, safety and preliminary efficacy of Luvelta in relapsed or refractory children with *CBFA2T3::GLIS2* AML and $\geq 5\%$ bone marrow (BM) involvement by morphology. The *CBFA2T3::GLIS2* fusion will be confirmed at Foundation Medicine by next generation sequencing (NGS). The trial will open in up to 35 centers across US, Europe, Canada and Australia and is actively enrolling. The initial part of the trial will test luvelta monotherapy at 3.5 mg/kg or 4.3 mg/kg administered IV every 2 weeks in a 28-day cycle. Bayesian sequential monitoring is used for safety monitoring. The study committees will review the data to identify the recommended phase 2 dose of luvelta which will then be tested in the second part of the trial. Children who achieve BM morphological complete response (CR) may proceed to allogeneic hematopoietic stem cell transplantation (HSCT) or continue single-agent luvelta for up to 2 years at the investigators' discretion. Patients without CR after 2 cycles of luvelta monotherapy may add chemotherapy (cytarabine +/- fludarabine or azacytidine) in cycle 3 and beyond. Post-HSCT maintenance therapy with luvelta monotherapy is also allowed for up to 2 years. The primary endpoint is morphologic CR defined as $<5\%$ AML blasts in BM with absolute neutrophil recovery to >1000 and platelets $>100{,}000$ and absence of extramedullary disease. Secondary endpoints include PK levels and assessment of anti-drug antibody formation, safety, EFS and overall survival. Rates of measurable residual disease-negative CR and FRα antigen levels pre- and post-luvelta will also be explored. Clinical trial information: NCT06679582. Research Sponsor: None.

TPS10075 Poster Session

Phase 1/2 study of zilovertamab vedotin in pediatric and young adult hematologic malignancies or solid tumors (LIGHTBEAM-U01A).

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Background: ROR1 is an oncofetal protein expressed in various blood and solid cancers. Zilovertamab vedotin (ZV) is an antibody-drug conjugate comprising a monoclonal antibody against ROR1, a proteolytically cleavable linker, and monomethyl auristatin E. LIGHTBEAM-U01A (NCT06395103) is a single-arm, open-label, phase 1/2 basket study designed to evaluate ZV in 4 disease cohorts: pediatric B-cell acute lymphoblastic leukemia (B-ALL), pediatric diffuse large B-cell lymphoma (DLBCL)/Burkitt lymphoma, pediatric neuroblastoma, and pediatric or young adult Ewing sarcoma. **Methods:** Pediatric participants (pts) are aged 0 to < 18 years; young adults are aged 18-25 years. Pts must have a confirmed diagnosis of B-ALL or DLBCL/Burkitt lymphoma per WHO criteria that has relapsed after ≥2 prior lines of therapy, or histologically confirmed neuroblastoma or Ewing Sarcoma that is refractory to frontline therapy. Pts with B-ALL must have ≥5% bone marrow blasts (M2 or M3), pts with DLBCL/Burkitt lymphoma must have radiographically measurable disease per IPNHL response criteria, and pts with neuroblastoma or Ewing sarcoma must have measurable disease per RECIST v1.1 (or MIBG-avid evaluable neuroblastoma). Pts aged ≤16 years must have a Lansky play-performance scale ≥50, pts aged > 16 to < 18 years must have a Karnofsky performance status of ≥50, and pts aged ≥18 years must have an ECOG performance status of 0 or 1. The study consists of 2 parts: dose escalation and confirmation (part 1) and efficacy expansion (part 2). Part 1 will enroll 3-12 pts per dose level. Also, ≥3 pts will be enrolled in 2 age groups: 1 to < 6 years and 6 to < 18 years. Pts will receive ZV at a starting dose of 2 mg/kg IV Q3W, escalating to 2.25 and 2.5 mg/kg or de-escalating to 1.75 mg/kg per a modified toxicity probability interval design-2. In part 2, eligibility will be expanded to ≥6 months for all cohorts and ≤25 years for Ewing sarcoma (if adequate safety and tolerability are shown, eligibility will expand to age 0 to < 6 months). In part 2, 10 pts will be enrolled in each cohort and will receive ZV at the preliminary RP2D determined in part 1. Disease assessments for pts with DLBCL/Burkitt lymphoma, neuroblastoma, or Ewing sarcoma will be performed Q8W for 6 months, then Q12W through 24 months, then Q24W through 5 years, then annually. Disease assessments for B-ALL will be performed at the end of each treatment cycle, at 6 months, at 1 year, then annually. Adverse events (AEs) will be monitored ≤30 days after last dose of study treatment (90 days for serious AEs; 30 days if new anticancer therapy is initiated) and will be graded per NCI CTCAE v5.0. Primary end points are safety and objective response rate. Secondary end points are pharmacokinetics, immunogenicity, duration of response, and eligibility for transplant/CAR-T therapy for pts with B-ALL or DLBCL/Burkitt lymphoma. Approximately 50-90 pts will be enrolled. Recruitment is underway. Clinical trial information: NCT06395103. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.