results of subjects treated at dose level 1 (DL1; 1 million GD2-CAR T-cells/kg IV). Methods: Four patients (3 DP1G, 1 spinal DMG; ages 4–25; 1M/3F) were enrolled at DL1. Three subjects with H3K27M+ DP1G received 116 GD2-CAR T-cells/kg IV on study. One patient with spinal DMG enrolled but became ineligible after manufacturing and was treated on an eND at DL1. An Omnnaya reservoir was placed in all subjects for therapeutic monitoring of intracranial pressure. Subjects underwent lymphodepletion with fludarabine, cyclophosphamide and external beam radiation therapy and loaded onto a MinION flow cell. Sequencing was performed for 3 hours and assessed for purity using NanoDrop spectrophotometer. DNA was then derived from 20 female and 30 male patients with a median age of 8 years. DNA and loaded onto a MinION flow cell. Sequencing was performed for 3 hours and assessed for purity using NanoDrop spectrophotometer. DNA was then derived from 20 female and 30 male patients with a median age of 8 years. DNA was extracted from nucleated blood. 3/4 patients exhibited marked improvement or resolution of neurologic deficits and radiographic improvement. The patient treated on an eND exhibited <90% reduction in spinal DMG volume but progressed by month 3. Re-treatment of this subject via intracerebroventricular administration resulted in a second reduction in spinal DMG volume by ~80%. Conclusions: GD2-CAR T-cells at DL1 demonstrate a tolerable safety profile in patients with H3K27M+ DP1G/DMG with clear signs of T-cell expansion and activity including clinical responses.

EPCIT-15. RAPID EPIGENOMIC CLASSIFICATION OF BRAIN TUMORS ENABLES INTRAOPERATIVE NEUROSURGICAL RISK MODULATION

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Background: Clear identification of tumor subtype is the main prerequisite for adequate level of surgical risk. At brain tumor resection, identifying malignancy and intraoperative histology often give an ambiguous diagnosis, complicating intraoperative surgical decision-making. Here, we report a nanopore DNA methylation analysis (NDMA) sequencing approach combined with single-cell analysis for classification of entities that could be used intraoperatively. Methods: We analyzed 50 biopsies obtained from biobanked tissue (43, prospective) or sampled at surgery (7, intraoperative) from 20 female and 30 male patients with a median age of 8 years. DNA was extracted from nucleated blood. 3/4 patients exhibited marked improvement or resolution of neurologic deficits and radiographic improvement. The patient treated on an eND exhibited <90% reduction in spinal DMG volume but progressed by month 3. Re-treatment of this subject via intracerebroventricular administration resulted in a second reduction in spinal DMG volume by ~80%. Conclusions: GD2-CAR T-cells at DL1 demonstrate a tolerable safety profile in patients with H3K27M+ DP1G/DMG with clear signs of T-cell expansion and activity including clinical responses.

EPCIT-17. DEVELOPING EYA PHOSPHATASE INHIBITORS WITH ON-TARGET EFFECTS IN SHH-MEDULLOBLASTOMA

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Medulloblastoma, one of the most frequent malignant pediatric brain tumors, encompasses four molecularly and clinically distinct cancers. Sonic hedgehog (SHH)-subtype medulloblastoma constitutes about 30% of medulloblastomas, and therapies targeting the SHH pathway can lead to new highly selective treatment. The halocid dehalogenase (HAD) phosphatase Eyes Absent 1 (EYA1) is critically involved in the development and progression of SHH-medulloblastoma: Eya1 is highly expressed in SHH-medulloblastomas, and single cell sequencing indicates that Eya1 is a consistent feature that can be detected in every individual cancer cell. Inhibition of EYA1 interrupts the SHH pathway signal, leading to tumor growth. During normal development, EYA1 promotes symmetric division of cerebellar granule cell precursors (GCPs), the cells of origin for SHH-subtype medulloblastoma, and reduced levels of EYA1 decrease medulloblastoma mortality rates in mouse models. Therefore, targeting EYA1 may be a novel therapeutic avenue for these pediatric cancers. Benzorone derivatives have been suggested as allosteric EYA-inhibitors, and benzorone provides a promising platform for chemical derivatives. Here, we develop 60 novel benzorone derivatives and assess their efficacy in inhibiting SHH-medulloblastoma growth through the inhibition of EYA1. Several of the new compounds inhibit EYA1, and inhibit SHH phosphorylation pathway in a cell-based assay, disrupt SHH pathway, and prevent SHH-medulloblastoma growth in vitro. Our results show that these novel benzorone derivatives are a new promising avenue for developing therapeutics for pediatric SHH-medulloblastoma via inhibition of EYA phosphatases.

EPCIT-18. A TWO-PART, PHASE 1 STUDY OF RHEUMIN-186 NANOLIPOSOME (186NL) DELIVERED BY CONVECTION ENHANCED DELIVERY FOR RECURRENT, REFRACTORY, OR PROGRESSIVE EPENDYMOMA AND HIGH-GRADE GLIOMA (HGG) AND NEWLY DIAGNOSED INFUSIVE INTRINSIC PONTINE GLIOMA (DIPG)

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Children with low-grade glioma have excellent survival rates but are often exposed to the morbidity of treatment, particularly from cytotoxic chemotherapies. Targeted agents appear to have some activity but the long-term effects of inhibiting normal developmental pathways are unknown. Lenalidomide is an oral immunomodulatory agent that has exhibited properties including anti-angiogenesis. Phase I studies indicated greater tolerability of this agent compared to adults, and a potential dose-response effect. We performed a Phase 2 trial of lenalidomide in children with pilocytic astrocytoma and optic pathway gliomas who failed initial therapy. The primary objective was to determine the objective response rate of children randomized to Regimen A low-dose (20 mg/m2/dose) or Regimen B high-dose (113 mg/m2/dose) lenalidomide, each administering lenalidomide daily for 21 days of each 28-day course. Secondary objectives included estimation of event-free survival (EFS) in this population and correlation of plasma lenalidomide concentration with toxicity and outcome.

Results: 74 eligible patients were enrolled (n=37 to each arm). The predefined activity level of interest was achieved for both arms. Objective responses were observed in both arms, with 4 partial responses in each. A total of n=18 patients completed 26 courses of therapy (Arm A, n=12, Arm B, n=6). The median number of courses on each arm was 14 (range 2–26) for Arm A and 11 for Arm B (range 1–26). Of the 74 eligible patients who received study drug, 30 required a dose reduction for toxicity (Arm A, n=8, Arm B, n=24) and 16 discontinued treatment on protocol due to toxicity (Arm A, n=2, Arm B, n=14). Conclusion: Lenalidomide demonstrates a sufficient level of activity in children with low-grade glioma to warrant further exploration in Phase 3 studies. Low-dose (20 mg/m2) lenalidomide appears to have better tolerability.

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the management of pediatric gliomas, it is limited by tolerance of the surrounding normal brain tissue. Rhenium-186 NanoLiposome (186RNLF) permits the selective delivery of beta-emitting radiation of high specific activity within the tumor. In a mouse model of medulloblastoma (NCT01906385), the mean absorbed dose to the tumor when coverage was 75% or greater (n=10) was 392 Gy (CI 306–478). Thus far, the therapy has been well tolerated, no dose-limiting toxicity has been observed, and 99 therapy-related serious adverse events have occurred despite markedly higher absorbed doses than typically delivered by EBRT (n=18).

Methods: This is a two-part, Phase I dose-finding study followed by an expansion cohort to explore efficacy. Part I will enroll up to 18 subjects to determine the maximum feasible dose to be evaluated. Part II of 186RNLF, administered by convection enhanced delivery (CED). Tumor size will be limited to a diameter of 4 cm in the longest axis and a volume of 34 mL. The dose limiting toxicity period (DLT) is 28 days post infusion. Part 2 will independently evaluate 186RNLF in 3 different cohorts: Cohort A: up to 12 subjects with a diagnosis of recurrent, refractory, or progression post-EBRT; Cohort B: up to 12 subjects with a diagnosis of recurrent, refractory, or progressive HGG; Cohort C: up to 15 subjects with newly diagnosed DIPG. The primary endpoint is overall response rate (ORR) by Radiographic Assessment in Pediatric Neuro-Oncology (RAPNO) criteria. Secondary endpoints are PFS-24 and OS-24 in Cohort A and PFS-12 and OS-12 in Cohorts B and C. Planned enrollment will begin in H2 2021.

EPTC-19. DRUG RESISTANCE IN MEDULLOBLASTOMA ADDRESSED WITH OLIG2 INHIBITOR, CT-179
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Patients with medulloblastoma, the most common malignant pediatric brain tumor, need improved treatment options. Conventional medulloblastoma treatment, with resection, chemotherapy, and radiation, leaves survivors at risk of neurocognitive injury, growth defects, and psychosocial impairment. Moreover, there is no effective therapy for recurrent medulloblastoma. We seek to identify novel treatments that will address systemic toxicity and tumor recurrence. We tested a nanoparticle formulation of the CDK4/6 inhibitor, palbociclib (Pox-palbo) in mice genetically-engineered to develop medulloblastoma (G-Smo mice) and found a significant anti-tumor effect that was consistently limited by the recurrence of OLIG2 in medulloblastoma stem cells. We then tested the hypothesis that directly targeting OLIG2 function would improve the efficacy of palbociclib and forestall resistance. We therefore examined the potential efficacy of CT-179, a first-in-class OLIG2 inhibitor, in G-Smo mice engineered to express luciferase as an SHH reporter. These studies showed that CT-179 decreased SHH signaling and prolonged event-free survival. Pharmacodynamic studies of G-Smo mice during treatment showed that CT-179 altered cell-cycle progression and promotes a shift towards cell-cycle arrest. Mechanistically, CT-179 decreased the Olig2 phosphorylation. The combination of CT-179 and Pox-palbo increased event-free survival of G-Smo mice compared to either agent administered alone. Our studies show both the potential of the palbociclib CT-179 combination, and the potential for CT-179 to improve the efficacy of therapies limited by Olig2+ stem cell recurrence. As Olig2+ stem cells have been shown to drive recurrence to conventional therapy and Olig2 phosphorylation disables p53-driven apoptosis, CT-179 may be a versatile agent to enhance both targeted and cytotoxic treatments.

EPTC-20. TECHNICAL FEASIBILITY SODIUM (23NA) MRI OF PEDIATRIC GLIOMAS
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Pediatric glioma response to novel targeted therapy can be heterogeneous on conventional proton (1H) MRI. Sodium concentration, as measured with 23Na MRI in adult brain tumors can provide complementary assessment of tumor proliferation to conventional MRI. However, 23Na MRI pediatric brain tumor studies are lacking. Determine the technical feasibility of performing sodium23Na MRI on pediatric glioma patients. Prospective study of an immunotherapy trial for newly diagnosed and recurrent gliomas (high-grade gliomas, low-grade gliomas, brainstem gliomas, and other), in which participants were imaged with 23Na MRI at 3.0 Tesla. The participants (n=26, 14 males) with a median age of 11 years (range = 1–23 years of age) were prospectively evaluated with sodium23Na MRI is technically feasible in the pediatric population and can distinguish different types of pediatric gliomas at baseline. Pediatric central nervous system tumors remain a leading cause of cancer-related death in children and adolescents. Safe sampling of tumor tissue for diagnostic purposes may be challenging. Subclinical detection of disease prior to clinical or imaging progression may provide opportunity for earlier intervention and ultimately improve overall survival. Additionally, our understanding of molecular evolution in response to therapy remains limited, given the rarity of serial sampling of tumor tissue. Methods: We report our experience with minimally invasive molecular diagnostics using a novel two-creation generation fluorine-19 ((2F) fluorine) cell-free DNA (cfDNA) obtained at the time of surgery, by intraventricular catheter or lumbar puncture. All CSF samples were collected as part of clinical care, and results reported to both clinicians and patients/ families: Results: We analyzed 64 CSF samples from 45 pediatric and adolescent and young adult (AYA) patients (pediatric=25; AYA=20) with primary and recurrent brain tumors across 12 histopathological subtypes including high-grade glioma (n=10), medulloblastoma (n=10), pineoblastoma (n=5), low grade glioma (n=4), diffuse leptomeningeal gliomatosis, (n=3), dermoeidermoid (n=4), metastatic retinoblastoma (n=4), ependymoma (n=3), and other (n=5). Somatic alterations were detected in 28/64 samples (44.4%) and in at least one sample per unique patient in 22/45 patients (48.8%). CSF cfDNA positivity was strongly associated with the presence of disease at the time of collection (86.3%). No association was seen between CSF cfDNA positivity and the timing of CSF collection during the patient’s disease course. Conclusion: We identified four general categories where CSF cfDNA may have added clinical utility: 1) diagnosis; 2) identification of actionable alterations; 3) track response to therapy; and 4) monitoring tumor evolution. Our findings support broader implementation of clinical CSF cfDNA testing in this population that may improve care.

EPTC-22. SAFETY AND EFFICACY OF INTRAVENTRICULAR IMMUNOONIOLOGY THERAPY WITH ONCOLYTIC HSV-1 G207 FOR TREATMENT OF LEPOMENINGEAL DISEASE
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Leptomeningeal metastatic disease (LMD) occurs in 30–50% of newly diagnosed and recurrent pediatric malignant cerebellar tumors and 20–30% of malignant supratentorial tumors. Recent advances in our understanding of tumor biology often cause substantial long-term neurotoxicity and outcomes remain poor for patients with LMD. At recurrence, LMD is generally minimally responsive to conventional therapies. Immunoooniotherapy with engineered oncolytic HSV-1:G207 has emerged as a promising treatment for children with high-grade brain tumors. G207 infects and kills tumor cells while sparing normal cells and stimulates a robust anti-tumor immune response. Intratumoral G207 inoculation demonstrated safety and preliminary efficacy in a pediatric Phase 1 trial in recurrent/progressive high-grade glioma (NCT02457845), and a Phase 2 trial (NCT04482933) is forthcoming. Additionally, a Phase 1 trial of intratumoral G207 in recurrent/progressive malignant pediatric cerebellar tumors is ongoing (NCT01931188). While intratumoral inoculation delivers G207 directly to a primary tumor, it requires neurosurgical procedures thereby limiting repeat doses. Thus, we sought to establish the safety and efficacy of intraventricular G207. Utilizing an immunocompetent, HSV-sensitive murine model of group 3 medulloblastoma including LMD. These findings provide support for a novel translation of intraventricular G207.