

the management of pediatric gliomas, it is limited by tolerance of the surrounding normal brain tissue. Rhenium-186 NanoLiposome (¹⁸⁶RNL) permits the selective delivery of beta-emitting radiation of high specific activity with excellent retention in the tumor. In a Phase 1 trial in adults with recurrent glioblastoma (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 no treatment-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 1 dose-finding study followed by an expansion cohort to explore efficacy. Part 1 will enroll up to 18 subjects to determine the maximum feasible dose (MFD) of ¹⁸⁶RNL 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 ¹⁸⁶RNL in 3 different cohorts: Cohort A: up to 12 subjects with a diagnosis of recurrent, refractory, or progressive ependymoma; 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.

EPCT-19. DRUG RESISTANCE IN MEDULLOBLASTOMA ADDRESSED WITH OLIG2 INHIBITOR, CT-179

Taylor Dismuke, Chaemin Lim, and Timothy Gershon; UNC-CH, Chapel Hill, NC, USA

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+ 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 alters 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.

EPCT-20. TECHNICAL FEASIBILITY SODIUM (23NA) MRI OF PEDIATRIC GLIOMAS

Aashim Bhatia; UPMC, Pittsburgh, PA, USA

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 sodium ²³Na 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) in which participants were imaged with ²³Na MRI at 3.0 Tesla. The participants (n=26, 14 males) with median age of 11 years (range = 4–23 years of age) were prospectively evaluated with sodium. ²³Na MRI is technically feasible in the pediatric population and can distinguish different types of pediatric gliomas at baseline.

EPCT-21. NEXT-GENERATION SEQUENCING OF CEREBROSPINAL FLUID FOR CLINICAL MOLECULAR DIAGNOSTICS IN ADOLESCENT AND YOUNG ADULT (AYA) BRAIN TUMOR PATIENTS

Alexandra Miller¹, Luca Szalontay², Nancy Bouvier¹, Hamza Ahmed¹, Katherine Hill¹, Johnathan Rafailov¹, Alex Lee¹, Irene Rodriguez-Sanchez¹, Onur Yildirim¹, Arti Patel¹, Tejus Bale¹, Ryma Benayed¹, Maria Arcila¹,

Maria Donzelli^{1,3}, Ira Dunkel^{1,3}, Stephen Gilheeny^{1,3}, Yasmin Khakoo^{1,3}, Kim Kramer^{1,3}, Sameer F. Sait Sait^{1,3}, Jeffrey Greenfield^{1,3}, Mark Souweidane^{1,3}, Sofia Haque¹, Audrey Mauguen¹, Michael Berger¹, Ingo Mellinger^{1,3}, and Matthias Karajannis^{1,3}; ¹Memorial Sloan Kettering Cancer Center, New York, NY, USA, ²Columbia University Irving Medical Center, New York, NY, USA, ³Weill Cornell Medical College, New York, NY, USA

Purpose: 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 validated next generation sequencing assay for sequencing of cerebrospinal fluid (CSF) 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 glioneuronal tumor (DLGNT) (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 disseminated 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 testing provided additional relevant diagnostic, prognostic, and/or therapeutic information, impacting clinical assessment and decision making: 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.

EPCT-22 SAFETY AND EFFICACY OF INTRAVENTRICULAR IMMUNOVIROTHERAPY WITH ONCOLYTIC HSV-1 G207 FOR TREATMENT OF LEPTOMENINGEAL DISEASE

Kyung-Don Kang¹, Joshua Bernstock², Bryan Mott¹, Li Nan¹, Rong Li³, Stacie Totsch¹, Sam Gary¹, Gelare Ghajar-Rahimi¹, Tina Etmann¹, Tanja Eisemann⁴, Robert Wechsler-Reya⁴, Elizabeth Beierle¹, George Gillespie¹, James Markert¹, Gregory Friedman¹; ¹University of Alabama at Birmingham, Birmingham, AL, USA, ²Brigham and Women's Hospital, Boston, MA, USA, ³Children's of Alabama, Birmingham, AL, USA, ⁴Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA

Leptomeningeal metastatic disease (LMD) occurs in 30–50% of newly diagnosed and recurrent pediatric malignant cerebellar tumors and 20–45% of malignant supratentorial tumors. Radiation and chemotherapy often cause substantial long-term neurotoxicity and outcomes remain poor for patients with LMD. At recurrence, LMD is generally minimally responsive to conventional therapies. Immunovirotherapy 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 (NCT03911388). 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 strain, we determined that a standard 1x10⁷ plaque-forming units (PFU) dose of G207 resulted in damage to the ependymal lining. However, interferon induction with an intraventricular low-dose (1x10⁴ PFU) of G207 or polyinosinic-polycytidylic acid (poly I:C), a toll-like receptor 3 agonist, three days prior to standard treatment dose protected the ependymal lining. This approach enabled safe delivery of multiple subsequent doses. Importantly, with these protective measures, G207 significantly prolonged survival in pediatric patient-derived xenograft models and an immunocompetent murine LMD model of group 3 medulloblastoma, the most aggressive and fatal subtype. Collectively, these data indicate that toxicity from intraventricular G207 can be safely mitigated prior to a therapeutic dose, and that intraventricular G207 effectively targets group 3 medulloblastoma including LMD. These findings provide support for clinical translation of intraventricular G207.