EPCT-06. A PHASE I STUDY OF MULTI-TARGETED THERAPY IN NEWLY DIAGNOSED OR PROGRESSIVE DIFFUSE INTRINSIC PONTINE GLIOMA

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BACKGROUND: Diffuse intrinsic pontine glioma (DIPG) constitutes 80% of pediatric brain stem tumors with a median survival of 12 months. The PI3K/AKT/mTOR pathway is a key oncogenic driver of this tumor. Targeting the chromatin dysregulation through HDAC inhibition, demonstrated benefit in vivo and vitro studies. We completed the first study as a multi-targeted therapy using SAHA and temsirolimus in pediatric DIPG. METHODS: After receiving institutional IRB approval, we enrolled 6 patients on this phase I study using a 3 + 3 statistical design. Patients were divided into stratum 1 and stratum 2, based on newly diagnosed or relapsed DIPG respectively. Stratum I patients received radiation therapy concurrently with vorinostat, followed by maintenance therapy with vorinostat and temsirolimus for 10 cycles (28 day cycle), while in stratum II patients received vorinostat and temsirolimus for 12 cycles. Neuroimaging including diffusion tensor imaging were evaluated where feasible. RESULTS: Three patients were enrolled in each of the stratum. One patient in stratum 1 completed therapy, 2 other demonstrated progressive disease (PD) after 4th and 1st cycle of maintenance therapy respectively. In stratum 2 all patients progressed 2 months after the start of therapy. However no dose-limiting toxicity (DLT) was noted. The patient in stratum 1 who completed therapy, remained free of PD 21 months after diagnosis with continued improvements in the volume of enhancing and T2 hyperintense disease. CONCLUSION: Although no significant benefit was seen as compared to historical controls during this study, no dose limiting toxicity was noticed with this treatment.

EPCT-07. DEBIO1347, AN ORAL FGFR INHIBITOR: RESULTS FROM A SINGLE CENTER STUDY IN RECURRENT/REFRACTORY FGFR ALTERED PEDIATRIC GLIOMAS

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BACKGROUND: Oncogenic driver alterations in FGFR are present in a subset of pediatric gliomas. Debio1347 is an orally available, highly selective FGFR 1–3 inhibitor that had a favorable safety profile and encouraging preliminary clinical activity in an adult phase 1 study. METHODS: Five children with progressive/refractory CNS tumors harboring an FGFR gene alteration following prior chemotherapy were treated with Debio1347 at Memorial Sloan Kettering Cancer Center on single patient use protocols. Patients were treated using the 20 mg tablet formulation at the adult recommended phase 2 dose (80 mg/1.73 m2 * BSA once daily). Toxicities were graded using CTCAEv5.0 and imaging response assessments were performed every 8–12 weeks. RESULTS: All AEs were grade 1–2. Most common treatment-related adverse events were ALT increased, hypoalbuminemia and hyperphosphatemia (4 patients). Two patients met criteria for partial response and two patients had stable disease. A 13 month-old patient with a spinal cord high-grade glioma harboring two FGFR1 mutations (V592M, K687) had tumor reduction of 91.7% maintained for 12 months. A 26-month-old patient with a pilomyxoid astrocytoma harboring an FGFR1-TACC1 fusion had a tumor reduction of 74.5% maintained for 9 months. Prolonged disease stabilization was noted in an eight year-old patient with metastatic suprasellar pilomyxoid astrocytoma harboring an FGFR1 mutation (9 months) and in a 14 year-old patient with posterior fossa glioneuronal tumor harboring an FGFR3-TACC3 fusion (18 months and ongoing). CONCLUSIONS: Debio1347 demonstrated tolerable toxicity and promising anti-tumor efficacy in pediatric patients with refractory FGFR altered gliomas. Further studies in this population are warranted.

EPCT-08. ACTIVITY OF LAROTRECTINIB IN PEDIATRIC TROPOMYOSIN RECEPTOR KINASE (TRK) FUSION CANCER PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM (CNS) TUMORS

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BACKGROUND: TRK fusions are oncogenic drivers in a variety of tumors, many involving the CNS. Larotrectinib, a selective FDA- and EMA-approved TRK inhibitor, demonstrated a 79% objective response rate (ORR) and a 35.2-month median duration of response (DoR) in adult and pediatric patients with various non-CNS solid tumors harboring *NTRK* gene fusions. We report the clinical activity of larotrectinib in pediatric patients with primary TRK fusion CNS tumors. METHODS: Patients aged <18 years with primary CNS tumors harboring an *NTRK* gene fusion detected by local molecular testing who were treated with larotrectinib in two clinical trials (NCT02637687, NCT02576431) were identified. Larotrectinib was administered until disease progression, withdrawal, or unacceptable toxicity. Disease status was investigator assessed (RANO). RESULTS: As of February 2019, 14 pediatric patients with primary TRK fusion CNS tumors were identified. Gene fusions involved *NTRK2* (n=10), *NTRK1* (n=2), and *NTRK3* (n=2). Median age was 7.0 years (range 1.3–16.7). ORR was 45% (95% CI 17–77%) among 11 evaluable patients. Two patients had complete responses (pending confirmation), three had confirmed partial responses, and six had stable disease. 24-week disease control rate was 73%. DoR ranged from 2.6+ to 5.5+ months and progression-free survival ranged from 0.03+ to 13.9+ months. Duration of treatment ranged from 0.03+ to 16.6+ months. Treatment-emergent adverse events were mainly grade 1–2. CONCLUSIONS: Larotrectinib resulted in objective responses and durable disease control in pediatric patients with primary TRK fusion CNS tumors. These results support expanded testing for *NTRK* gene fusions in patients with CNS tumors.

EPCT-09. CLR 131 IN PATIENTS WITH RELAPSED OR REFRACTORY PEDIATRIC MALIGNANCIES

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BACKGROUND: CLR 131 is a novel targeted radiotherapeutic that exploits the selective uptake and retention of phospholipid ethers by malignant cells. CLR 131 selectively delivers radiation to malignant tumor cells, thus minimizing radiation exposure to normal tissues. OBJECTIVE: CLR 131 is being examined in a Phase 1 trial, CLOVER-2 (NCT03478462), to determine the safety, tolerability, and initial efficacy of CLR 131 in children and adolescents with relapsed/refractory malignancies. METHODS: Eligibility criteria include children with relapsed or refractory solid tumors or malignant brain tumors for which there are no standard treatment options with curative potential. Subjects must be between ages 2 and 21 with no limit to the number of prior therapies. CLR 131 is administered as a single infusion in escalating doses beginning at 15 mCi/m^2. Adverse events (AEs) are graded by NCI-CTCAE v5. RESULTS: As of 10Jan2020, four subjects with brain tumors have received CLR 131; one at 15 mCi/m^2 and three at 30 mCi/m^2. Diagnoses included DIPG (2), glioblastoma (1), and medulloblastoma (1). Median age is 13 years (range 10–15) and patients received a median of two prior therapies (range 1 to 8). There were no treatment emergent AEs at the 15 mCi/m^2 dose level attributed to CLR 131 by the investigator. Assessment of the 30 mCi/m^2 dose level is ongoing. CONCLUSIONS: CLR 131 is a unique, first in class targeted radiotherapeutic for pediatric malignancies. Preliminary data shows an acceptable and expected safety profile in this patient population. Dose escalation to determine the highest tolerated dose is ongoing.

EPCT-11. PHASE 1 STUDY OF FLUVASTATIN-CELECOXIB COMBINATION IN CHILDREN WITH RELAPSING/REFRACTORY OPTICO-CHIASMATIC LOW-GRADE GLIOMA OR HIGH-GRADE GLIOMAS (FLUVABREX): FINAL RESULTS

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BACKGROUND: Preclinical data support the activity of celecoxib and fluvastatin in high grade (HGG) and low grade gliomas (LGG). A Phase I study was designed to evaluate this combination in children with re-