fractory/relapsed glioma. AIM: To assess the safety, pharmacokinetics (PK), maximum tolerated dose, Recommended Dose for Phase II (RDP2). METHOD: Multicenter phase I trial, including patients aged 6 to 21 year old. Fluvastatin starting dose was 2 mg/kg/day, 14/28 days, with fixed dose of celecoxib (200–800 mg /day). Four dose levels of fluvastatin (2, 4, 6, 8 mg/kg/day) were evaluated. A Continual Reassessment Method was used for dose escalation. Dose-limiting toxicities (DLT) were determined on the 1st cycle. PK samples were obtained at D1 and D14 of cycle 1, pre-dose of cycle 2. RESULTS: 20 patients were enrolled with a median age of 12 years (5.9–19). They previously received a median of 3 (1–7) lines of treatment. Ten patients were treated for LGG and 10 for HGG, receiving a median of 3.5 cycles (1–21). Patients with LGG received a median of 9 cycles (1–21). Among the 17 patients evaluable for DLT, 2 DLTs were reported: 1 grade 3 maculo-papular rash (4 mg/kg), and 1 grade 4 increase of CPK (6 mg/kg). The RP2D of fluvastatin is 6 mg/kg/day. CONCLUSION: In children with refractory/relapsed glioma, the RDP2 of fluvastatin associated with celecoxib is 6 mg/kg/day. This combination is well tolerated encouraging a phase 2 study in LGG.

EPCT-12. PNOC015: PHASE 1 STUDY OF MTX110 (AQUEOUS PANOBINOSTAT) DELIVERED BY CONVECTION ENHANCED DELIVERY (CED) IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) PREVIOUSLY TREATED WITH RADIATION THERAPY

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OBJECTIVE: To determine safety and distribution of MTX110 delivered by CED in newly diagnosed DIPG patients. METHODS: DIPG patients (3–21 years) were enrolled after radiation. CED of MTX110 combined with gadoteridol was completed based on dose levels (DL) (30–90 µM with volumes ranging from 3 cc (single dose) to 2 consecutive doses of 6 cc; total number of DL=7). Catheter position was chosen to maximize tumor coverage. Distribution of infusate was monitored with real-time MR imaging. Repeat CED was performed every 4–8 weeks if tolerated. Quality of life (QOL) assessments using PedsQL Generic Core and Brain Tumor modules were obtained at baseline (n=5), 3-months (n=3), and end of therapy (n=2). Single-cell RNA sequencing and analysis of histone modifications was performed to assess pharmacodynamic effects on DIPG cells. RESULTS: Between May 2018-Dec 2019, 6 patients were enrolled (median age 8 years, range 5–21). Dose limiting toxicities included: grade 3 gait disturbance (DL7; cycle 1); grade 3 muscle weakness/vagus nerve disorder (DL5; cycle 4) and grade 2 intolerable dysphagia (DL7; cycle 4). Twelve CED procedures were completed at DL7 and repeated cycles ranged from 2 to 7. Infusion to distribution volume ratio was approximately 1:3.5. There were no significant changes in self-reported QOL. Parent ratings of patients' worry ($p = 0.04$) and overall QOL ($p = 0.03$) significantly decreased at 3-months. CONCLUSION: Repeat CED of MTX110 at the highest dose is tolerable. Tissue concentrations are likely to be substantially higher compared to oral dosing. Pharmacodynamic effects will be presented.

EPCT-13. CMV PP65 RNA-PULSED DENDRITIC CELL VACCINES FOR PEDIATRIC GLIOBLASTOMA AND MEDULLOBLASTOMA: PHASE I TRIAL RESULTS

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BACKGROUND: Recurrent medulloblastoma and malignant glioma are lethal tumors that are virtually incurable. The cytomegalovirus (CMV) antigen pp65 is ubiquitously expressed on medulloblastoma and malignant glioma but not on healthy brain. We evaluated autologous CMV pp65 RNA-pulsed dendritic cell (DC) vaccines in children and young adults in a phase I trial. METHODS: Circulating monocytes were harvested using leukapheresis, differentiated into DCs, matured, and pulsed with pp65 RNA using electroporation. DCs were packaged into vaccines ($2x10^7$DC/vaccine) and administered intradermally following tetanus-diphtheria toxoid site preconditioning every 2 weeks x3, then monthly. The primary objectives of the study were to establish the feasibility of generating at least 3 vaccines and safety. An exploratory objective was to evaluate the ability of vaccination to create and enhance patient pp65-specific T cell responses. RESULTS: Eleven patients were enrolled with medulloblastoma (n=3) or glioblastoma (n=8). Ages ranged from 9–30 years old (mean 15.5y). Ten of 11 patients (91%) generated at least 3 vaccines (mean 6.2). Eight patients received at least 3 vaccines. To date, 4 patients have received all generated vaccines without progression, 4 patients have progressed, and 2 patients are still receiving vaccines. There have not been any severe adverse events probably or definitely related to vaccines. More mature data will be presented at ISPNO. CONCLUSIONS: Leukapheresis and monocyte differentiation is a feasible strategy for generating adequate DCs for active immunization in children with malignant brain tumors. CMV pp65 RNA-pulsed DCs are well-tolerated and immunogenic. Efficacy endpoints will be evaluated in a subsequent phase II trial.

EPCT-15. THE REMIND TRIAL: MULTI-ANTIGEN TARGETED T CELLS FOR PEDIATRIC CNS TUMORS

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BACKGROUND: Patients with relapsed CNS malignancies or DIPG face terrible prognoses. We hypothesized that T cells specific for 3 tumor-associated antigens (TAA), WT1, PRAME and survivin, would be safe and elicit anti-tumor immunity. METHODS: Patients (n=9) have received autologous tumor antigen-associated T cells (TAAT) (up to $4x10^7/m^2$) for newly diagnosed DIPG (Group A) or recurrent CNS malignancies (Group B) on a Phase I dose-escalation study (NCT03652545) and were monitored for safety and response. RESULTS/DISCUSSION: 9/9 patients who received TAAT completed the 45-day safety monitoring phase with no dose-limiting toxicities. Infused cells were predominantly CD3+ T cells (median 96%; range: 87–99%), with CD4+ and CD8+ comprising 16% (range: 5–87%) and 40% (range: 4–67%) of the CD3+ cells, respectively. TAAT with specificity for 1–3 TAAs, at varying frequencies, was demonstrated in 8/9 TAAT by anti-IFN-γ ELISPOT. Plasma cytokine profiles demonstrated infusion-related immune cytokine responses. In summary, TAAT are safe and may elicit anti-tumor responses in vivo. To confirm TAAT-driven effects, we are evaluating plasma proteomic profiles for immune-response signatures and assessing unique T cell receptor rearrangements of infused TAAT. Response assessment and dose escalation are ongoing.

EPCT-16. A PHASE IB STUDY OF PTC596 IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA AND HIGH GRADE GLIOMA

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BACKGROUND: BMI-1 is highly expressed in DIPG. Downregulation leads to inhibition of cell proliferation, cell cycle signaling, self-renewal, telomerase expression, activity, and suppression of DIPG cell migration. Targeted inhibition of BMI-1 sensitizes DIPG cells to radiation and drug-induced DNA damage. PTC596 (formulated by PTC Therapeutics, Inc.) is a novel, orally available drug that inhibits microtubule polymerization, resulting in G2/M cell cycle arrest and post-translational modification of BMI-1 protein and reduced BMI-1 protein levels. OBJECTIVES: To estimate the maximum tolerated dose and describe dose limiting toxicities, pharmacokinetics and pharmacodynamics of PTC596 in children 3–21 years of age with newly diagnosed diffuse intrinsic pontine glioma and high-grade gliomas. METHODS: PTC596 is administered twice per week orally during radiotherapy and as maintenance for up to two years. The starting dose of PTC596 was 200 mg/m^2, with a subsequent dose level of $260mg/m^2$/dose. Pharmacokinetics are performed in Cycles 1 and 2. RESULTS: This study is currently ongoing. Nine patients (7 with DIPG, 2 with HGG), 8 evaluable, have been enrolled. At dose level 1, 200 mg/m^2, three evaluable patients were enrolled and experienced no DLTs. At dose level 2, among 5 evaluable patients, 2 experienced dose-limiting grade 4 neutropenia. PTC596 has been otherwise well tolerated. Five patients remain in Cycles 2–11. CONCLUSION: This phase I trial is ongoing. PTC596 is tolerable at dose level 1. We

are amending the protocol to introduce tablets that can be dissolved in liquid to allow enrollment of younger patients and those unable to swallow whole tablets.

EPCT-17. A PHASE I AND SURGICAL STUDY OF RIBOCICLIB AND EVEROLIMUS IN CHILDREN WITH RECURRENT OR REFRACTORY MALIGNANT BRAIN TUMORS: PEDIATRIC BRAIN TUMOR CONSORTIUM INTERIM REPORT

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Genomic aberrations in the cell cycle and PI3K pathway are commonly observed in recurrent childhood brain tumors. Dual inhibition of CDK4/6 (ribociclib) and mTOR (everolimus) has strong biologic rationale, non-overlapping single-agent toxicities, and adult clinical experience. The maximum tolerated dosage (MTD) and/or recommended phase two dose (RP2D) of ribociclib and everolimus was determined in the Phase I study and ribociclib concentrations were characterized in plasma and tumor in children undergoing neurosurgical procedures. Following resection, eligible patients were enrolled in the Phase I study according to a rolling 6 design and received ribociclib and everolimus once daily for 21 days and 28 days, respectively. Patients undergoing surgery received ribociclib at the pediatric RP2D (350 mg/m^2/day) for 7–10 days pre-operatively. Pharmacokinetic samples were collected on both cohorts and analyzed in nine patients on phase I study. Sixteen eligible patients enrolled on phase I study (median age 10.3 years; range: 3.9–20.4) and 5 patients were enrolled on the surgical cohort (median age 11.4 years; range: 7.2–17.1). Six patients enrolled at dose level 1 without dose limiting toxicities (DLT). Two of the three patients at dose level 2 experienced DLT (grade 3 hypertension and grade 4 ALT). The most common grade 3/4 toxicities were lymphopenia, neutropenia, and leucopenia. Everolimus concentrations following administration of everolimus alone were lower than those following drug combination, suggesting an impact of ribociclib on everolimus pharmacokinetics. The MTD/RP2D of ribociclib and everolimus in recurrent CNS tumors is 120 mg/m^2 and 1.2 mg/ m^2 daily for 21 days and 28 days, respectively.

EPCT-18. PHASE 0/I STUDY OF GM-CSF AND INTRATHECAL TRASTUZUMAB IN CHILDREN WITH RECURRENT POSTERIOR FOSSA EPENDYMOMA

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BACKGROUND: Posterior fossa ependymoma (PF EPN) is a pediatric central nervous system malignancy that has a poor outcome to standard therapeutic approaches. The majority of PF EPN tumors have increased HER2 expression. Trastuzumab is a monoclonal antibody that targets HER2, and sargramostim (GM-CSF) stimulates hematopoietic progenitor cell proliferation. The combination of trastuzumab and GM-CSF has been shown to trigger antibody-dependent cell cytotoxicity in vitro in PF EPN cell lines. METHODS: Children aged 1–21 years with relapsed PF EPN and no ventriculoperitoneal shunt or CSF obstruction are eligible for the Phase 0/I institutional trial at Children's Hospital Colorado. Stratum 1 involves IT trastuzumab and subcutaneous (subQ) GM-CSF prior to standard-of-care surgical resection. Stratum 2 involves a 3 + 3 phase I design with serial IT trastuzumab doses, each preceded by three days of GM-CSF, to establish the MTD for IT trastuzumab. RESULTS: Trastuzumab was detected in a sufficient number of tumors after presurgical IT delivery in Stratum 1 to open Stratum 2. Four patients (75% female) have been enrolled in Stratum 2 at trastuzumab Dose Level 1. Median age at enrollment is 9.8 years (range, 3.5–20.2 years). Preliminary CSF pharmacokinetic analysis demonstrated detectable trastuzumab up to 14 days after IT doses. No dose-limiting toxicities have occurred. Two patients progressed on therapy (median, 4 cycles). One patient is progression-free at 18 months off therapy. One patient remains on study therapy. CONCLUSIONS: IT trastuzumab penetrates PF EPN tumor tissue. Stratum 2 remains open to accrual at Dose Level 2.

EPCT-19. A PHASE I STUDY OF RIBOCICLIB AND EVEROLIMUS FOLLOWING RADIATION THERAPY IN CHILDREN WITH NEWLY DIAGNOSED NON-BIOPSIED DIFFUSE PONTINE GLIOMAS (DIPG) AND RB+ BIOPSIED DIPG AND HIGH GRADE GLIOMAS (HGG)

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Genomic aberrations in the cell cycle and mTOR pathways have been reported in diffuse pontine gliomas (DIPG) and high-grade gliomas (HGG). Dual inhibition of CDK4/6 (ribociclib) and mTOR (everolimus) has strong biologic rationale, non-overlapping single-agent toxicities, and adult clinical experience. The maximum tolerated dose (MTD) and/or recommended phase two dose (RP2D) of ribociclib and everolimus administered during maintenance therapy following radiotherapy was determined in the phase I study as a rolling 6 design. Ribociclib and everolimus were administered once daily for 21 days and 28 days, respectively starting two-four weeks post completion of radiotherapy. All HGG patients and any DIPG patient who had undergone biopsy were screened for RB protein by immunohistochemistry. Eighteen eligible patients enrolled (median age 8 years; range: 2–18). Six patients enrolled at dose levels 1,2, and 3 without dose limiting toxicities (DLT). Currently, five patients are enrolled at dose level 3 expansion cohort. The median number of cycles are 4.5 (range: 1–20+). Among the expansion cohort, one dose limiting toxicity included a grade 3 infection and one patient required a dose reduction in course 3 due to grade 3 ALT and grade 4 hypokalemia. The most common grade 3/4 adverse events included neutropenia. Preliminary pharmacokinetic studies on 12 patients suggest an impact of ribociclib on everolimus pharmacokinetics. The MTD/RP2D of ribociclib and everolimus following radiotherapy in newly diagnosed DIPG and HGG is anticipated to be 170 mg/m^2/day x 21 days and 1.5 mg/ m^2/day every 28 days which is equivalent to the adult RP2D.

EPENDYMOMA

EPEN-01. MULTIDISCIPLINARY TREATMENT IN EPENDYMOMA

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BACKGROUND: In intracranial ependymoma, the effectiveness of chemotherapy and radiation therapy is unclear, and the degree of tumor removal contributes to the improvement of life prognosis. METHODS: We examined ependymoma cases treated in our institution from July 1998 to March 2017. RESULTS: There were 18 boys and 7 girls. The average age at the time of surgery is 5.3±3.6 years. The pathological diagnosis was Grade II for 8 cases and Grade III for 17 cases. Genetic analysis was performed in 16/25 cases (64%). Of the infratentorial cases, 10/11 cases (90.1%) were PFA and PFB were one case. Of the supratentorial cases, 3/5 cases (60%) were positive for RELA fusion. As chemotherapy, 19 patients were VCR + VP-16 + CDDP + CPA. Irradiation was performed in all cases, local irradiation (50.4–55.8Gy) in 22 cases (88%), and craniospinal irradiation in 2 cases (8%). The 7-year OS was 74.6±9% and the 7-year PFS was 59.7±10.5%. Grade III showed a short OS ($p = 0.053$). GTR and NTR were obtained in the first excision in 14 cases (56%), and OS and PFS were not significantly different from those in the STR group ($p = 0.219$, $p = 0.248$). GTR and NTR including 2nd-look surgery were obtained in 18 cases (72%), and significant improvement of OS was observed compared with STR group ($p = 0.02$). CONCLUSION: Even if it is not GTR or NTR at the first operation, improvement of OS is expected by total excision after chemotherapy.

EPEN-02. EVALUATION OF TREATMENT OUTCOMES AND EXPRESSION OF EMT-RELATED TRANSCRIPTION FACTORS AS NOVEL THERAPEUTIC TARGETS IN PEDIATRIC EPENDYMOMA

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OBJECTIVE: Intracranial ependymomas are common brain tumors in children. However, prognosis, especially in young children, remains poor because of the chemo- and radioresistant properties of intracranial ependymomas. Furthermore, effective treatments for intracranial ependymomas remain a challenge. The epithelial-to-mesenchymal transition