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