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

(EMT) is important for invasion and metastasis in many cancers. This study aimed to evaluate and compare treatment outcomes with the expression of EMT-related transcription factors in pediatric ependymomas. MATERIAL AND METHODS: Medical and radio-imaging data of 22 (11 boys, 11 girls) patients aged <15 years with intracranial ependymomas were reviewed from January 1983 to December 2018. Six cases were subdivided into clinicopathological-molecular subgroups and immunohistochemically analyzed for Slug and ZEB. RESULTS: The median age at the start of treatment was 5 years (range 8 months–15 years) (9 cases were aged <3 years). The median progression-free survival (PFS) was 25.6 (range, 0.8–383.5) months; the median overall survival (OS) was 81.9 (range, 2.9–383.5) months. Extent of resection and malignant histology were significant prognostic factors for OS and PFS in multivariate analysis. There were 6 cases (2 cases of PFA, 2 of PFB, 1 of ST and 1 case of ST-RELA). Nuclear expression of ZEB1 was found in all tumors; however, that of Slug increased only in PFA and PFB tumors, which were associated with a poor prognosis. CONCLUSION: Expression of EMT-related transcription factors was increased in pediatric ependymomas. These data suggest that EMT is a novel therapeutic target for treating pediatric intracranial ependymomas.

EPEN-03. LONG-TERM FOLLOW-UP OF AIEOP 2ND SERIES OF CHILDREN AND ADOLESCENT WITH PRIMARY INTRACRANIAL (ST:SUPRATENTORIAL; PF: POSTERIOR FOSSA) EPENDYMOMA AND METHYLATION GROUPS RE-ANALYSES

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BACKGROUND: This 2002–2014 Italian prospective study stratified 160 patients by surgical resection (complete=NED/incomplete=ED) and centrally-reviewed grade. Grade2/NED patients received focal radiotherapy (RT) up to 59.4Gy, Grade3/NED received 4 courses of VEC(vincristine,etoposide,cyclophosphamide) after RT.ED patients received 1–4 VEC courses, second-look surgery, 59.4 Gy+8Gy boost on measurable residue. METHODS: We re-analyzed data at 115 months follow-up including methylation profile on available samples. RESULTS: Global PFS/OS at 5/10 years were 66/59% and 80/74%, respectively. Of the 64 relapsers at median 20 months, 53 died at median 37/18 months after diagnosis/relapse, respectively.10/64 relapsed after 5 years (66–126 months); 4 died, relapse was local in 8/10, metastatic 1, combined 1;5/10 patients were below age 3, 5 females, 8 PF tumors. Their survival post-relapse was not longer than earlier relapsers'. At univariable analysis, age over 3 years, female sex, complete surgery, grade 2, no shunt confirmed better PFS/OS. 66/95 analyzed tumors received a score >0.80 through the DNA methylation-based central nervous system tumor classifier: 41/8 as PFA/PFB, respectively,14/17 ST as RELA-positive (3 scored for other molecular entities i.e. anaplastic PXA, LGG MYB, HGNET). Prognostic factors were equally distributed among PFA/PFB groups,1 only group B patient relapsed locally at 96 months. CONCLUSIONS: Already published prognostic factors remained at long-term follow-up;6.2% patients had late relapses. OS after relapse was not better in late relapsers. Group B confirmed better prognosis but all patients had received «at least» adjuvant RT. Modern ependymoma trials need long follow-up to draw firm conclusions.

EPEN-04. ONCOGENIC 3D TUMOR GENOME ORGANIZATION IDENTIFIES NEW THERAPEUTIC TARGETS IN EPENDYMOMA

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By profiling enhancers in primary ependymoma tumors, we have recently identified putative oncogenes, molecular targets, and functional pathways. Inhibition of selected targets diminished the proliferation of patient-derived neurospheres and increased survival in mouse models of ependymoma. While enhancers frequently regulate the nearest gene, identification of enhancer target genes remains to be a challenge in the absence of chromosome conformation information. Consequently, we have now used HiC to map the 3-dimensional organization of tumor chromatin in the two most common and aggressive ependymoma subgroups: posterior fossa group A (PF-EPN-A) and supratentorial ependymomas with gene fusions involving the NF-κB subunit gene RELA (ST-EPN-RELA). By an integrative analysis of enhancer and gene expression in the context of the newly derived HiC data, we find that a large number of the predicted enhancer target genes are enriched for strong physical interactions. Importantly, we also identify many new putative tumor-dependency genes activated by long-range promoter-enhancer interactions and complex tumor-specific chromatin clusters of regulatory elements. Complementary to the analysis of gene-enhancer interactions, we have also leveraged the HiC data for resolving structural rearrangements underlying copy number alterations. Copy number gains of the 1q arm of chromosome 1 are especially associated with poor survival. Our preliminary results in PFA relapse samples show complex structural variants underlying 1q gain that lead to inter-chromosomal rearrangements and affect several genes that potentially contribute to poor survival. In ongoing work we are testing the relevance of the novel candidate genes for tumor cell growth and proliferation in-patient derived ependymoma models.

EPEN-05. CLINICAL AND GENETIC EVOLUTION OF EPENDYMOMA EXPOSED FROM A MULTI-RECURRENCE GIRL CASE

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Ependymomas are glial brain tumors accounting for approximately 2~3% of all primary tumors of the central nervous system (CNS), and 12% of all pediatric intracranial tumors. To better understand the evolution process of ependymomas, we studied the clinical, pathological and genetic development of a rare girl case with repeatedly recurrent ependymoma. This girl was diagnosed as ependymoma at age of 9 years old, and experienced 7 times tumor relapse and received 9 times surgeries but finally ceased at 19 years old with multiregional recurrences. The pathological characteristics, radiographic images and therapeutic strategies of the patient were all retrieved. Molecular markers confirmed the diagnosis of anaplastic ependymoma based on the updated WHO guideline for CNS tumors. Whole-genome sequencing (WGS) was performed to elucidate the landscape of mutation signatures and to identify potential driver mutations along the tumor progression. The seven tumor specimens showed a highly branched evolutionary pattern. There were six gene mutations found in 5 of the 7 specimens (PCDHA4, PCDHA8, SEC14L6, SETD2, RIOK2, and SLCO2A1) and three