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Diffuse intrinsic pontine glioma (DIPG) is a fatal pediatric brain tumor with no curative treatments. Approximately 80% of DIPGs contain an H3K27M mutation. The implications of the mutation and how they may be targeted are not fully understood. We established an H3K27M effect-isolating model by transducing H3K27-wildtype lines (HSJD-GBM-001, normal human astrocytes) with lentiviral-packaged H3K27M. We characterized H3K27M-related changes through western blot, phenotypic assays, and RNA-seq. Drug screening of H3K27-wildtype and matched H3K27M-transduced lines was used to identify targets more effective with H3K27M present. Patient-derived pediatric glioblastoma and DIPG lines (BT-245, SU-DIPG-IV, HSJD-DIPG-007, SU-DIPG-XIII*, SF7761) were used for validation. We observed increased H3K27ac and decreased H3K27me3, as well as increased proliferative and migratory abilities, with the addition of H3K27M to H3K27-wildtype lines. RNA-seq showed downregulation of cell cycle regulation and upregulation of epithelial-mesenchymal transition. GSK1070916, an Aurora kinase B/C inhibitor, was isolated from a synthetic lethality screen with H3K27M. GSK1070916 showed strong efficacy in native H3K27M lines (IC_{50}s=60nM-1250nM), superior to the Aurora kinase A inhibitor alisertib, to which all cell lines showed substantial resistance. Combination of both drugs was not synergistic. GSK1070916 treatment caused increased H3K27me3 and decreased H3S10ph and H3S28ph. GSK1070916 induced apoptosis and S-phase stall. The H3K27M mutation induces epigenetic, phenotypic, and cell cycle regulation changes resulting in relaxation of transcriptional controls and more aggressive growth. Aurora kinase B/C inhibition is a novel therapeutic modality for DIPG that appears capable of reversing some H3K27M-related epigenetic changes, inducing apoptosis, and repressing uncontrolled cellular division.

DIPG-80. CLINICAL AND RADIOGRAPHIC RESPONSE TO ONC201 IN A PEDIATRIC PATIENT WITH A THALAMIC H3K27M AND BRAFV600E MUTANT DIFFUSE MIDLINE HIGH GRADE GLIOMA

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Recent improved understanding of the molecular markers of high grade glioma has shifted the approach to these aggressive CNS tumors to increasingly use molecularly guided targeted therapies. Treatment of patients with BRAFV600E mutant high grade gliomas with BRAF inhibitors has shown efficacy, however the impact of concomitant H3K27M mutation is unknown. ONC201 targets dopamine receptor D2 (DRD2), which is shown to be broadly overexpressed in the thalamus as well as multiple tumor types; its antagonism has demonstrated anti-tumor efficacy and immunomodulatory properties in preclinical studies. ONC201 has also demonstrated clinical efficacy in patients with H3K27M mutant gliomas. We present the case of a 9-year-old male with a right thalamic H3.3K27M mutant diffuse midline glioma with a concomitant BRAFV600E mutation with an ongoing partial response to ONC201 treatment. The patient was diagnosed in May 2018. He underwent biopsy, followed by standard focal proton radiation therapy (54Gy) and subsequent treatment with dasatinib, bevacizumab and everolimus over the course of five months. After continued radiographic progression on serial imaging, in April 2019 he started ONC201 375mg orally once per week through an expanded access trial. He has tolerated the medication well with grade 1 nausea and fatigue. Over the next nine months, he demonstrated clinical and radiographic improvement with modest increased use of his left side and MRIs showing progressive decrease in size of the thalamic lesion with a 70 % decrease in the target lesion (measuring 53x62mm prior to treatment, decreased to 38x26mm in January 2020).

DIPG-82. CLINICAL EXPERIENCE OF CONVECTION ENHANCED DELIVERY (CED) OF CARBOPLATIN AND SODIUM VALPROATE INTO THE PONS FOR THE TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) IN CHILDREN AND YOUNG ADULTS AFTER RADIOTHERAPY

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PURPOSE: Effective treatment of diffuse intrinsic pontine glioma (DIPG) remains a formidable challenge due to inadequate penetration of the blood-brain barrier (BBB) by systemically administered chemotherapies. The BBB can be overcome by directly infusing drugs into pons using method of convection-enhanced delivery (CED). We describe our clinical experience and what we have learned about the safety and feasibility of treating DIPG with intermittent CED of carboplatin and sodium valproate to the pons through the Renishaw Drug Delivery System (RDDS). METHODS: Retrospective review (2017–2020) of children with DIPG, who following radiotherapy, received compassionate treatment commencing 3.3–10 months post diagnosis (median 4.9 months). They received up to 7 cycles of 3–6 weekly pontine infusions of carboplatin (0.12-0.18mg/ml) and sodium valproate (14.4- 28.8mg/ml). RESULTS: 13 children 3–19 years (mean 6.9 years) were treated. There were no surgical complications. With the exception of infusion channels blocking in one device there were no adverse device effects. Two patients developed persistent 6th nerve palsies, which led to drug concentration reduction in the combination therapy. Subsequently infusion/ drug related toxicities were transient. Tumour was controlled in pons in 11/13 patients. Median progression free survival (PFS) was 13.0 months, while median overall survival (OS) was 15.3 months. CONCLUSIONS: Use of the RDDS was safe and well tolerated in all 13 patients. Treatment improved control of pontine disease resulting in longer PFS and OS than reported for conventional therapy and merits further evaluation in a clinical trial.

DIPG-83. USING COPPER CHELATING AGENTS TO TARGET RECEPTOR TYROSINE KINASE SIGNALLING IN DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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DIPG is a universally fatal pediatric brain cancer. Receptor tyrosine kinase (RTK) pathway alterations are among the defining characteristics in many patients. Copper is a transition metal essential for cellular signaling, known to impact PI3K/AKT and MAPK/ERK pathways. Copper chelating agents are clinically approved for use in children with Wilson's Disease, documented to reduce brain copper levels and are cited as potential cancer therapeutics. Due to copper's wide cellular integration, we propose that targeting copper in DIPG through use of copper chelators is a viable therapeutic strategy and are strong candidates for combination therapy. Cytotoxicity assays performed in a panel of DIPG cell lines using copper chelator tetraethylenepentamine (TEPA) demonstrated a millimolar range of efficacy. To identify copper integrated pathways, western blots were performed on DIPG cell lines dosed with sub-lethal copper concentrations, which increased phosphorylated expression of AKT, ERK1/2, ERK5 and STAT3. Conversely, western blots performed after TEPA treatment demonstrated reduced phosphorylated expression of all these proteins compared to controls. Western blots investigating TEPA in combination with Everolimus and Trametinib demonstrated synergistic targeting of these proteins. Our results indicate that adding copper in the culture media initiated two RTK-mediated downstream signal transductions, including AKT and ERK and additionally STAT signaling. The use of copper chelator TEPA affected copper homeostasis and reduced DIPG cell proliferation. Our study proposes copper plays an important role in RTK-mediated signaling promoting DIPG proliferation. This implies that reducing copper with clinically available chelation agents can represent a potential anti-cancer treatment for DIPG.

DIPG-84. COMPLEMENTARY AND ALTERNATIVE MEDICINE IN DIFFUSE INTRINSIC PONTINE GLIOMA

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INTRODUCTION: Diffuse intrinsic pontine glioma (DIPG) is a rare and aggressive childhood brainstem malignancy with a two-year survival rate of ≤10%. In this international survey study we aim to evaluate the use of complementary and alternative medicine (CAM) in this patient population. METHODS: Parents of-, and physicians treating DIPG patients were asked to participate in a retrospective online survey with questions regarding CAM use during time of illness. RESULTS: 120 parents and 75 physicians contributed to the online survey between January and May 2020. Physicians estimated that <50% of their patients used CAM, whereas 69% of the parents reported to have used CAM to treat their child during time of illness. Cannabis was the most widely used form of CAM, followed by vitamins and minerals, melatonin, curcumin and boswellic acid. CAM was mainly used to actively treat the tumor. Other motivations were to treat side effects of chemotherapy, or to comfort the child. Children diagnosed ≥2016 were more likely to use CAM ($\chi 2$=6.08, p=0.014). No significant difference was found between CAM users and non-users based on ethnicity ($\chi 2$=*4.18*, p=0.382) and country of residence ($\chi 2$=*9.37*, p=0.154). Almost 50% of the physicians do not frequently ask their patients about possible CAM use. CONCLUSION: This survey demonstrates that worldwide a considerable number of DIPG patients use CAM. Physicians should be more aware

of potential CAM use and more actively discuss the topic. More research is needed to gain knowledge about possible anticancer effects of CAM and their interactions with conventional therapies.

EARLY PHASE CLINICAL TRIALS

EPCT-01. PHASE I STUDY OF DAY101 (TAK580) IN CHILDREN AND YOUNG ADULTS WITH RADIOGRAPHICALLY RECURRENT OR PROGRESSIVE LOW-GRADE GLIOMA (LGG)

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BACKGROUND: We report a phase I study examining pharmacokinetics, safety and recommended dosage of the type 2 RAF inhibitor DAY101 in children/young adults with radiographically recurrent/progressive LGGs harboring MAPK pathway alterations. METHODS: Applying a 3 + 3 design, patients < 18 years of age with radiographically recurrent/progressive LGG received oral DAY101 weekly for 4-week cycles up to a maximum of 2 years, if deriving clinical benefit. The starting DAY101 dosage was 280 mg/m^2. Dose limiting toxicities were determined after one cycle. RESULTS: We treated nine eligible patients at 280, 350, and 420 mg/m^2. Eight patients had KIAA1549:BRAF fusions. One patient with NF1 did not have a biopsy. There were no DLTs. Weekly administration of DAY101 in children resulted in dose-proportional increases in C_{max} and AUC similar to that described in adults. A 2.2-fold mg/kg exposure difference was observed with respect to weight-based dosing and suggested a correlation to best radiographic RANO responses of 2 complete responses, 2 partial responses, 3 stable disease, and 2 progressive disease (independently-reviewed). Median time to response was 10.5 weeks (range: 8–32 weeks). CONCLUSION: The phase 1A data provide initial pharmacokinetic parameters to describe oral weekly dosing of DAY101 in pediatric patients with radiographically recurrent/progressive LGG. Plasma exposures of DAY101 achieved in adults can be reached in pediatric patients. Oral weekly DAY101 is well-tolerated and possesses anti-tumor activity. The amended protocol will explore additional dose levels and the potential for differential dosing to achieve similar responses across a variety of BSAs.

EPCT-02. PBTC-051: FIRST IN PEDIATRICS PHASE 1 STUDY OF CD40 AGONISTIC MONOCLONAL ANTIBODY APX005M IN PEDIATRIC SUBJECTS WITH RECURRENT/REFRACTORY BRAIN TUMORS

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BACKGROUND: CD40 is a co-stimulatory molecule expressed on antigen presenting cells (APCs). APX005M is a CD40 agonist monoclonal antibody which stimulates innate and adaptive anti-tumor immunity through activation of APCs, macrophages, and antigen-specific CD8$^+$T-cells. Pediatric Brain Tumor Consortium study PBTC-051 is the first investigation of APX005M in pediatric patients and is evaluating the safety, recommended phase 2 dose (RP2D), pharmacokinetics, and preliminary efficacy of APX005M in children with central nervous system (CNS) tumors. RESULTS: Accrual of patients with recurrent/refractory primary malignant CNS tumors (stratum 1) began in March 2018. 16 patients (2 ineligible) have enrolled on this stratum; 14 were treated. Dose escalation through 3 planned dose levels of APX005M was completed without excessive or unanticipated toxicities. The highest dose level (0.6 mg/kg q3 weeks) is the presumptive RP2D, and an expansion cohort is currently enrolling at this dose. 2 patients at dose level 3 have received >12 cycles of therapy. Grade 3 or higher adverse events at least possibly attributable to APX005M include 11 lymphopenia, 5 neutropenia, 5 leukopenia, 3 ALT elevations, 1 AST elevation, 1 thrombocytopenia, and 1 hypoalbuminemia. PK data will be available March 2020. Stratum 2 is now enrolling patients with post-radiation/pre-progression DIPG beginning at dose level 2, with 1 patient currently enrolled. CONCLUSION: The CD40 agonistic antibody APX005M has demonstrated preliminary safety in pediatric patients with recurrent/refractory primary malignant CNS tumors and has a likely RP2D of 0.6 mg/kg q3 weeks in this population. Preliminary efficacy data are pending.

EPCT-03. A PHASE I TRIAL OF 2-HYDROXYOLEIC ACID IN PEDIATRIC PATIENTS WITH ADVANCED CENTRAL NERVOUS SYSTEM TUMORS

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2-hydroxyoleic acid (2-OHOA) is the first potential anti-cancer drug to act by modification of cell membrane lipid content. The agent is a derivative of oleic acid, a naturally occurring component of olive oil. Through its unique mechanism of activating sphingomyelin synthase 1, 2-OHOA targets the membrane lipid composition of cancer cells. These lipid changes alter membrane-dependent signaling cascades, such as the Ras/MAPK pathway, that promote tumor cell proliferation. A comprehensive pre-clinical program has characterized the safety and effects of 2-OHOA across a host of animal models. A European phase I/IIa trial of 2-OHOA in adult patients has shown initial promising results with five refractory high-grade glioma patients demonstrating objective clinical benefit by RANO criteria for six or more months. The drug has been very well-tolerated in adult patients with minimal toxicity. This phase I study is the first pediatric investigation of 2-OHOA and focuses on the treatment of relapsed/refractory pediatric central nervous system (CNS) tumors. The trial consists of a dose-escalation phase in up to 18 patients using a standard "3 + 3" design, followed by an expanded safety cohort of up to 10 patients treated at the maximum tolerated dose to confirm the recommended phase II dose. Due to the promising clinical results in adult neuro-oncology patients and the widespread involvement of the Ras/MAPK pathway and other membrane-dependent signaling cascades in the development of pediatric malignancies, we hypothesize that 2-OHOA may be a safe and effective treatment for pediatric patients with several types of advanced CNS tumors.

EPCT-05. A PHASE I TRIAL OF THE CDK 4/6 INHIBITOR PALBOCICLIB IN PEDIATRIC PATIENTS WITH PROGRESSIVE OR REFRACTORY CNS TUMORS: A PEDIATRIC BRAIN TUMOR CONSORTIUM (PBTC) STUDY

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PBTC-042 was a phase I trial of palbociclib to determine the maximum tolerated dose (MTD) and describe toxicities in children. Palbociclib is an oral, selective cyclin dependent kinase 4/6 inhibitor. METHODS: A rolling-6 design was utilized. Eligible patients were children ≥4 and ≤21 years-old with a progressive/refractory CNS tumor with intact retinoblastoma protein, measurable disease, and ability to swallow capsules. Pharmacokinetic studies were performed during the first course. Here, we report on the heavily pretreated stratum, which included patients who received >4 prior treatment regimens (either chemotherapy or biologic agent), and/or craniospinal irradiation, and/or myeloablative chemotherapy plus stem cell rescue. Palbociclib was initiated at 50 mg/m^2/day for 21 consecutive days of a 28-day course. This was one dosage level below the MTD for the less heavily pretreated stratum (75 mg/m^2). RESULTS: Fourteen eligible patients were enrolled (median age 12.8 years; male 79%). Eleven patients (79%) had either ependymoma or medulloblastoma. Four eligible and evaluable patients were enrolled at 50 mg/m^2 with no DLTs. This prompted a dosage increase to 75 mg/m^2. Ten eligible subjects were enrolled and 7 were evaluable for DLT assessment. One of 7 evaluable patients experienced a DLT (grade 3 thrombocytopenia). This established 75 mg/m^2 as the MTD for more heavily pretreated patients. Mean ± SD palbociclib apparent oral clearance was 34.6 ± 18.4 L/h/m2. CONCLUSION: The MTD for palbociclib on a 3 week on/1 week off schedule in children with brain tumors is 75 mg/m^2 and does not appear to be influenced by the degree of prior therapy.