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Diffuse midline glioma (DMG) with the H3K27M mutation is a lethal childhood brain cancer, with patients rarely surviving 2 years from diagnosis. We conducted a multi-site Phase 1 trial of the imipridone ONC201 for children with H3K27M-mutant glioma (NCT03416530). Patients enrolled on Arm D of the trial (n=24) underwent serial lumbar puncture (baseline, 2, 6 months) for cell-free tumor DNA (cf-tDNA) analysis at time of MRI. Additionally, patients on all arms of the trial at the University of Michigan underwent serial plasma collection. CSF collection was feasible in this cohort, with no procedural complications. We collected 96 plasma samples and 53 CSF samples from 29 patients, including those with H3F3A (H3.3) (n=13), HIST13HB (H3.1) (n= 4), and unknown H3 status/not biopsied (n=12) [range of 0–8 CSF samples and 0–10 plasma samples]. We performed digital droplet polymerase chain reaction (ddPCR) analysis and/or amplicon-based electronic sequencing (Oxford Nanopore) of cf-tDNA samples and compared variant allele fraction (VAF) to radiographic change (maximal 2D tumor area on MRI). Preliminary analysis of samples demonstrates a correlation between changes in tumor size and H3K27M cf-tDNA VAF, when removing samples with concurrent bevacizumab. In multiple cases, early reduction in CSF cf-tDNA predicts long-term clinical response (>1 year) to ONC201, and does not increase in cases of later-defined pseudo-progression (radiation necrosis). For example, a now 9-year old patient with thalamic H3K27M-mutant DMG underwent treatment with ONC201 after initial radiation and developed increase in tumor size at 4 months post-radiation (124% baseline) of unclear etiology at the time. Meanwhile, her ddPCR declined from baseline 6.76% VAF to <1%, which has persisted, with now near complete response (15% tumor reduction) at 30 months on treatment from diagnosis. In summary, we present the feasibility and utility of serial CSF/plasma monitoring of a promising experimental therapy for DMG.

EPCT-04. RESULTS OF A PHASE 1 STUDY OF THE ONCOLYTIC ADENOVIRUS DNX-2401 WITH RADIOTHERAPY FOR NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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Background: A Phase 1, single center study is ongoing to evaluate the conditionally replicative oncolytic adenovirus, DNX-2401 (tasadenoturev), followed by radiotherapy (RT) in pediatric patients with newly diagnosed diffuse intrinsic pontine glioma (DIPG). Methods: Patients 1–18 years with newly diagnosed DIPG with no prior treatment, Lansky/Karnofsky performance score ≥ 70, and adequate organ function were enrolled. A tumor biopsy was performed followed by a single intratumoral injection of 1e10-5e10 virus particles (vp) DNX-2401. Conventional radiotherapy was initiated within 1 month of DNX-2401 administration. Results: Enrolled subjects (n=12) had a median age of 9 (range 3–18) and performance scores of 90–100 (n=4; 33%) or 70–80 (n=8; 67%). As part of a dose escalation design, subjects were treated with 1e10 vp (n=4) or 5e10 vp DNX-2401 (n=8), which was then followed by standard RT in 11 of 12 subjects (92%). No dose-limiting toxicities were observed and the treatment regimen was well-tolerated. Adverse events (AEs) have been primarily mild to moderate and consistent with underlying disease. The most commonly reported AEs (≥ 5 subjects), regardless of study drug relationship, include headache, asthenia, vomiting, anemia, leukocytosis, and fever. Two SAEs have been reported including grade 3 lymphopenia and grade 3 abdominal pain. Tumor reductions have been observed and efficacy evaluations are ongoing. As of 09Dec2020, 12-month survival (OS-12) was 71% and 4 of 12 patients had survived > 20 months. Four subjects continue to be followed for survival. Correlative analysis of tumor biopsy and peripheral samples is ongoing. Conclusions: DNX-2401 followed by RT can be safely administered to pediatric subjects with newly diagnosed DIPG; clinical activity and preliminary survival are encouraging.

EPCT-05. A PHASE 1/2 STUDY OF AVAPRITINIB FOR KIT- OR PDGFRA-MUTANT PEDIATRIC RELAPSED/REFRACTORY SOLID TUMORS

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Prognosis for pediatric patients with advanced relapsed/refractory (R/R) solid (including central nervous system [CNS]) tumors is poor; targeted therapies achieve response rates of only ~15%. Germ cell tumors and high-grade glioma (HGG) are the most common with *KIT* mutations; sarcoma and HGG are the most common tumors with platelet-derived growth factor receptor alpha (*PDGFRA*) mutations. Two-year overall survival is <10% for pediatric patients with diffuse intrinsic pontine glioma, often driven by *PDGFRA* mutations. No KIT/PDGFRA targeted therapies are currently approved for pediatric patients with R/R solid tumors. The selective KIT and PDGFRA inhibitor, avapritinib, demonstrated potent activity against KIT activation-loop (exon 17), juxtamembrane (exon 11), and extracellular-domain (exon 9) mutants (IC_{50} <2 nM), and PDGFRA activation-loop (D842V) mutants (IC_{50}=0.24 nM). CNS penetration in preclinical models (brain-to-plasma ratios at steady-state ranging from 0.74–1.00) demonstrated potential for activity against CNS tumors. Avapritinib is approved for the treatment of adults with unresectable/metastatic gastrointestinal stromal tumors (GIST) harboring *PDGFRA* exon 18 mutations (including D842V) in the USA based on an overall response rate ³84% with 59% response durations >6 months, and in the EU for adults with unresectable/metastatic GIST harboring a *PDGFRA* D842V mutation. The objectives of this 2-part phase 1/2 multicenter, open-label study, anticipated to enroll 31 patients from Q3 2021, are to assess avapritinib safety, preliminary efficacy, and pharmacokinetics in pediatric patients with KIT/PDGFRA-mutant solid R/R tumors. Eligible patients are aged 2 to <18 years with no alternative treatment options. Part 1 will enroll ≥6 patients; primary endpoint is confirmed age and body surface area physiologically-based pharmacokinetic modeling dose to provide equivalent exposure to the 300 mg adult avapritinib dose. Part 2 will enroll ≥25 patients at the recommended modeled avapritinib dose from Part 1; primary endpoint is overall response rate. Avapritinib once-daily will be administered in continuous 28-day cycles.

EPCT-06. PRECISION ONCOLOGY IN THE PEDIATRIC TARGETED THERAPY 2.0 PROGRAM

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Introduction: Precise diagnoses and robust detection of actionable alterations is required for individualized treatments. By using extended molecular

diagnostics, the Pediatric Targeted Therapy (PTT) 2.0 program aims at the improvement of diagnostic accuracy and detection of actionable alterations for pediatric high-risk patients. The impact of these analyses on clinical management is reported. Methods: Pediatric patients with relapsed or progressive tumors after standard of care treatment were included, independent of histological diagnosis. Formalin fixed paraffin embedded material and a blood sample for germline correction were requested. DNA methylation array, targeted gene panel sequencing (130 genes), RNA and Sanger sequencing in selected cases, and immunohistochemistry (IHC) of selected markers (pERK, pAKT, pS6, PD-L1) were performed. A questionnaire-based follow-up was used to determine the clinical impact of the analysis. Results: We enrolled n=263 patients from February 2017 to February 2019. Complete molecular analysis was possible for n=260 cases (99%). The most common entities were brain tumors (n=172/260, 65%). In brain tumors, DNA methylation array alone allowed robust diagnostic classification (score of >=0.9) in n=104/172 cases (60%). Actionable targets as detected by copy number calculation, gene panel sequencing, RNA sequencing and IHC were found in n=94/172 (55%) brain tumor cases. The most common actionable targets in brain tumors were MAPK (pERK, BRAF fusions, BRAF V600E), mTOR (pS6), PI3K (pAKT), CDK4/6 (CDKN2A/B loss), and immune checkpoints (PD-L1). Pathogenic germline alterations with clinical relevance were identified in n=12/172 brain tumor cases (6.9%) and were confirmed by Sanger sequencing, 5/12 (41%) of which were previously unknown. Clinical follow-up of subsequent treatment and outcome are ongoing. Conclusion: The combination of next-generation diagnostics such as methylation arrays and targeted sequencing in addition to selected IHC markers added robust information with regard to diagnosis and actionable alterations. The impact on clinical decision-making and on outcome is currently being evaluated.

EPCT-07. ID1 IS A KEY TRANSCRIPTIONAL REGULATOR OF DIPG INVASION AND IS TARGETABLE WITH CANNABIDIOL

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Diffuse intrinsic pontine gliomas (DIPGs) are lethal pediatric brain tumors with no effective therapies beyond radiation. The highly invasive nature of DIPG is key to its aggressive phenotype, but the factors and mechanisms contributing to this aggressive invasion are unknown. Inhibitor of DNA binding (ID) proteins, key regulators of lineage commitment during embryogenesis, are implicated in tumorigenesis in multiple human solid tumors. Prior work showed that recurrent *H3F3A* and *ACVR1* mutations increase ID1 expression in cultured astrocytes. However, the impact and targetability of ID1 have not been explored in human DIPG. Exome and transcriptome sequencing analyses of multi-focal DIPG tumors and normal brain tissue from autopsy (n=52) revealed that ID1 expression is significantly elevated in DIPG samples. Higher ID1 expression correlates with reduced survival in DIPG patients and increased regional invasion in multi-focal autopsy samples. Analyses of developing mouse brain RNA/ChIP-Seq data revealed high ID1 expression and H3K27ac promoter binding in prenatal hindbrain compared to all other prenatal and postnatal brain regions. ChIP-qPCR for H3K27ac and H3K27me3 revealed that *ID1 gene* regulatory regions are epigenetically poised for upregulation in DIPG tissues compared to normal brain, regardless of *H3/ACVR1* mutational status. These data support that the developing pons is regionally poised for *ID1* activation. Genetic (shRNA) *ID1* knockdown of primary human H3.3K27M-DIPG cells (DIPG007) resulted in significantly reduced invasion/migration and significantly improved survival of K27M-DIPG mice. Knockdown of ID1 in DIPG cells also resulted in down-regulation of the WNK1-NKCC1 pathway, which regulates tumor cell electrolyte homeostasis and migration. Finally, treatment of DIPG007 cells with cannabidiol (CBD) reduced ID1 levels, viability of DIPG cells and significantly improved survival of K27M-DIPG mice. In summary, our findings indicate that multifactorial (genetic and regional) epigenetic upregulation of *ID1* drives DIPG invasiveness; and that targeting *ID1* with CBD could potentially be an effective therapy for DIPG.

EPCT-08. TRIAL WORKING GROUPS FOR PAEDIATRIC BRAIN TUMOURS

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Introduction: Brain tumours are the biggest cancer killer in children and young adults. Several recent developments have the potential to change the treatment of brain tumours in children. These include ultrasound-mediated blood-brain barrier disruption, convection enhanced delivery, polymer delivery systems and electric field therapy, as well as intra-arterial, intra-CSF and intra-nasal chemotherapy. To date, there have been very few clinical trials to evaluate any of these. The science and technology underlying these developments is not traditionally embedded within the standard paediatric neuro-oncology network. In addition, custom-built hardware, novel surgical procedures and, in some cases, the testing and licensing of implantable devices, add difficulty at the regulatory level. Methods: The authors participated in an international workshop funded by the charity Children with Cancer UK in 2016, where different experimental techniques aimed at optimising CNS drug delivery were discussed. Following this workshop and two subsequent workshops run by the CBTDDC (Children's Brain Tumour Drug Delivery Consortium) in 2018 and 2020, the CBTDDC and the recently developed ITCC (Innovative Therapies for Children with Cancer) brain tumour group started working together to set up a new initiative. This aims to develop CNS-delivery-focused trial working groups for paediatric brain tumours. Results: We have assembled a prestigious steering group, comprising international researchers and clinicians with expertise in diverse aspects of translational and clinical research in CNS drug delivery. At our first group meeting in March, participants will discuss the most effective ways of translating the emerging drug delivery modalities into clinical trials. Prioritised actions will be taken forward and the group will reconvene to discuss developments and next steps at a workshop in the Autumn. Conclusion: We present this abstract to the SNO Paediatric conference to raise awareness of this initiative with the large number of relevant stakeholders who will be attending the event.

EPCT-09. CNS LEVELS OF PANOBINOSTAT IN A NON-HUMAN PRIMATE MODEL: COMPARISON OF BLOOD AND CEREBROSPINAL FLUID PHARMACOKINETIC METHODS AND MALDI MSI

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Adequate exposure (effective concentration over time) of a therapeutic agent at its site of action is essential for antitumor efficacy. Given constraints of repeat tissue sampling, non-human primate models predictive of pharmacokinetics in pediatric patients have been utilized to assess central nervous system (CNS) exposure. Assessment of cerebrospinal fluid (CSF) drug levels have been used to extrapolate CNS penetration but the relationship of CSF drug levels with tissue distribution is unclear. Utilizing microdialysis, we previously demonstrated geographic variability of drug permeability across the blood:brain barrier (BBB), but this technique is complex and has a high standard deviation. We, therefore, explored a novel technique, matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI MSI), to compare plasma, CSF, and tissue drug levels in a terminal non-human primate model. Panobinostat, an HDAC inhibitor in clinical trials for DIPG/DMG, was selected for study as it has previously demonstrated poor CNS tissue penetration but suggested modest clinical activity.

Methods: Panobinostat (p.o., dose 1.6 mg/kg) was administered to non-tumor bearing primates (n=2). One hour following administration (Tmax), blood and CSF were collected, the animal euthanized, brain and spinal cord extracted, and immediately frozen at -80. Panobinostat distribution was mapped on *ex vivo* sagittal tissue sections using MALDI MSI. To provide specificity and degree of permeability, anatomical structures were segmented for analysis to determine drug concentrations. Blood, CSF and tissue levels of panobinostat were measured via LC-MS/MS. Results: Segmentation analysis revealed quantifiable panobinostat, particularly in the lateral ventricles and choroid plexus, and also in the subventricular zone and brainstem, although the overall panobinostat concentration was below the limit of quantitation in these areas. Conclusions: Although not reflected in CSF PK, panobinostat is widely distributed in brain tissue. MALDI MSI allows regional assessment of panobinostat penetration and complements CSF pharmacokinetics.

EPCT-10. 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 prelim-