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Background: CNS tumors are the most common solid tumors and the deadliest cancers in children. Approximately 10% of children with a CNS tumor harbor a hereditary cancer syndrome (HCS), but many will not be tested for a HCS. The Utah Population Database (UPDB) contains comprehensive cancer registry data for Utah families and can determine multigenerational cancer pedigrees across an archive of 5.8 million individuals. We hypothesize that the UPDB can identify children and families with HCSs not previously identified. Methods: We queried the UPDB for individuals ages 0–39 diagnosed with a primary CNS tumor (malignant and benign) between 1966–2017 and generated cancer pedigrees of 3 generations or more for probands, extending to at least third-degree relatives. Specialized software calculated a familial standardized incidence ratio (FSIR) to determine families with excess clustering of CNS tumors. Clinical cancer genetics experts reviewed pedigrees to confirm patterns of HCS. Results: We identified 4,634 CNS tumors in 4,550 individuals, of whom 2,233 (49%) reside in high-quality pedigrees containing ≥2 grandparents, at least 1 from both maternal and paternal sides. To identify families with excess clustering of CNS tumors, we selected pedigrees with an FSIR $P<0.05$ and ≥2 affected patients, resulting in 161 high-risk families with a mean of 170 (median 96) relatives per pedigree of 3–6 generations. Among these 161 families, there were 2,017 unique relatives (first-third degree) of CNS probands with 2,355 tumors (any site), for a per pedigree average of 14.7 tumors in 12.5 relatives. Review of the 10 highest risk pedigrees indicated that 4 meet HCS criteria, including Li-Fraumeni (n=2), von Hippel-Lindau (n=1), and rhabdoid tumor predisposition (n=1). Conclusion: The UPDB can produce multigenerational cancer pedigrees that identify individuals and families at risk of harboring a HCS who warrant germline testing. These findings should encourage clinicians to perform thorough family history screening.

RARE-25. DISSECTING THE CONTEMPORARY EPIDEMIOLOGY OF PRIMARY AND SECONDARY BRAIN TUMORS IN INFANCY THROUGH CHILDHOOD

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Introduction: Herein we utilize national registry data to evaluate the epidemiology of primary and secondary pediatric brain tumors according to the WHO2016 classification. Methods: Pediatric patients (age≤14) presenting between 2004–2017 with a brain tumor were identified by ICD-O-3 and brain metastasis (2010–2017) coding from the National Cancer Database (comprising >70% of newly-diagnosed cancers in the U.S.), and categorized by NICHD age stages: infant (<1yr; n=1,686), toddler (1-2yrs; n=1,732), early- (2-5yrs; n=6,712), middle- (6-11yrs; n=9,175), and late- (12-14yrs; n=5,042) childhood. Patients' age, sex, race/ethnicity, and overall survival, and tumor location and size were evaluated by WHO2016 tumor type. Results: 24,347 pediatric brain tumor patients were identified. Overall, other astrocytic tumors (24% of females, 20% of males), diffuse astrocytic/oligodendroglial gliomas (23% of females, 21% of males – 64% of which were midline), embryonal (13% of females, 19% of males), and sellar region tumors (12% of females, 8% of males) predominated. Embryonal tumors prevailed in infancy (24%) and toddlerhood (24%), declining to 9% in late childhood; only 40% were female. Ependymal tumors peaked at 15% in toddlerhood (6% overall), whereas choroid plexus tumors peaked at 11% in infancy (1.9% overall). A minority of brain tumors were of neuronal & mixed neuronal-glial (6.1%), germ cell (3.8%), cranial nerve (3.2%), mesenchymal non-meningothelial (2.4%), meningioma (1.6%), pineal (1.1%), hematological/histiocytic (0.5%), and other glioma (0.2%) types. Brain metastases were rare (1.5% overall; from 4.0% in infancy to 0.8% in late childhood; and only 41% were female) – 61% came from adrenal neuroblastoma, 16% from sarcomas, and 6% from malignant rhabdoid tumors/extracranial AT/RT. Conclusions: Pediatric brain metastases overwhelmingly originate from adrenal neuroblastoma. Although, overall, diffuse astrocytic/oligodendroglial, other astrocytic, embryonal, and sellar region tumors predominate among pediatric brain tumors, together they only comprise 70% of cases and their distribution varies substantially by patients' age and sex.

TRANSLATIONAL/EARLY PHASE CLINICAL TRIALS

EPCT-01. A NOVEL PEPTIDE VACCINE DIRECTED TO CMV PP65 FOR TREATMENT OF RECURRENT MALIGNANT GLIOMA AND MEDULLOBLASTOMA IN CHILDREN AND YOUNG ADULTS: PRELIMINARY RESULTS OF A PHASE I TRIAL

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Introduction: The cytomegalovirus (CMV) antigen, pp65, is ubiquitously expressed in malignant glioma and medulloblastoma but not in healthy brain. The objective of this Phase I trial (NCT03299309) was to assess the safety and feasibility of a novel pp65 peptide vaccine (PEP-CMV) in children and young adults with recurrent medulloblastoma and malignant glioma. Methods: Vaccines contain a synthetic long peptide (SLP) of 26 amino acids encoding multiple potential class I, class II, and antibody epitopes of CMV pp65 across several haplotypes. This SLP is administered as an emulsion in Montanide ISA 51. Patients receive a single course of temozolomide to induce lymphopenia, tetanus/diphtheria toxoid site preconditioning, then vaccines administered intradermally every two weeks for 3 doses, then monthly. Results: To date, 22 patients have been enrolled. Diagnoses include medulloblastoma (n=2), glioblastoma (n=12), anaplastic oligodendroglioma (n=2), anaplastic astrocytoma (n=3), and malignant glioma NOS (n=3). Mean number of prior treatment regimens is 4.9 (range 1–12). Mean age is 22yo (range 6–35) and 45% of patients are male. The median KPS is 80. The median number of vaccines given at time of analysis is 3.3 (range 1–12). There have been no ≥ 3 Grade toxicities related to the vaccine. One patient developed nausea, vomiting, palpitations, and tachycardia after vaccination and had elevated inflammatory cytokines consistent with cytokine release syndrome. Median PFS is 2.5 months (95% CI: 1.7,4.5) and median OS is 6.5 months (95% CI 3.3, 7.9). Immune response to pp65 as determined by ELISpot was found in 75% of patients. On MRI 6 of the 11 evaluable patients have had at least stable disease with three of those having a partial response. Conclusions: Preliminary results demonstrate that PEP-CMV is well-tolerated and elicits an immune response in heavily pretreated, multiply recurrent patients. A multi-institutional Phase II trial is scheduled to open fall 2021.

EPCT-02. COMPARISON OF TARGETED AGENTS RECOMMENDED BY THE CNS-TAP TOOL TO THOSE SELECTED BY A TUMOR BOARD IN A MOLECULARLY-DRIVEN DIPG CLINICAL TRIAL

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Recently, sequencing of diffuse intrinsic pontine glioma (DIPG) biopsy specimens has revealed genomic heterogeneity of these tumors, fueling an interest in individualized, targeted treatment options. The Pacific Pediatric Neuro-Oncology Consortium recently completed enrollment onto a feasibility study PNOC003: Molecular Profiling for Individualized Treatment Plan for DIPG (NCT02274987), in which a multidisciplinary tumor board recommended molecularly-targeted agents based on genomic and molecular profiling of each patient's tumor. Separately, our group developed the Central Nervous System Targeted Agent Prediction (CNS-TAP) tool, which combines pre-clinical, clinical, and CNS penetration data with patient-specific genomic information to allow for numeric scoring of targeted anticancer agents to objectively evaluate these therapies for use in patients with CNS tumors. We hypothesized that highly-scored agents within CNS-TAP would overlap with the agents recommended by the tumor board in this study. For each PNOC003 participant, we utilized the genomic report to identify actionable alterations and input patient-specific data into CNS-TAP to identify the highest scoring agents. We compared high-scoring agents within CNS-TAP with recommendations from the PNOC003 tumor board for each of the enrolled 28 subjects. Overall, 93% (26/28) of patients had at least one agent recommended by both the tumor board and CNS-TAP. Additionally, 38% (37/95) of all agents recommended by the tumor board were also selected by CNS-TAP. Furthermore, we identified factors that likely contributed to the discordance between these two methods. Without clinician input, CNS-TAP is unable to account for drug-drug interactions, includes only designated anticancer agents, and cannot easily be updated in real time. However, CNS-TAP provides an objective evaluation of targeted therapies, whereas tumor boards are inherently subjective. Given the discordance identified between these methods and the strengths of each, a prospective study incorporating both CNS-TAP and a molecular tumor board for targeted therapy selection in DIPG patients is warranted.

EPCT-03. SERIAL PLASMA AND CSF CELL-FREE TUMOR DNA (CF-TDNA) TRACKING IN DIFFUSE MIDLINE GLIOMA PATIENTS UNDERGOING TREATMENT WITH ONC201

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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