Amy K. Bruzek[1], Jack Wadden[1], Clarissa May Babilla[1], Abed Rhaman Kawakibi[1], Sunjong Ji[1], Johanna Ramos[1], Alyssa Paul[1], Ian Wolfe[1], Marcia Leonard[1], Partricia Robertson[1], Andrea Franson[1], Rajen Mody[1], Hugh Garton[1], Yazmin Odia[3], Cassie Kline[4], Nicholas A. Vitanza[5], Soumen Khatua[6], Sabine Mueller[7], Joshua E. Allen[2], Sharon Gardner[8], and Carl Koschmann[1]; [1]Michigan Medicine, Ann Arbor, MI, USA, [2]Chimerix, Durham, NC, USA, [3]Miami Cancer Institute, Miami, FL, USA, [4]Children's Hospital of Philadelphia, Philadelphia, PA, USA, [5]Seattle Children's Hospital, Seattle, WA, USA, [6]University of Texas MD Anderson Cancer Center, Houston, TX, USA, [7]University of California San Francisco, San Francisco, CA, USA, [8]NYU Langone Health, New York, NY, USA

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)

Marc Garcia-Moure[1,2], Jaime Gállego Pérez-Larraya[1,3], Ana Patiño[1,2], Marisol Gonzalez-Huarriz[1,2], Chris Jones[4], Alan MacKay[4], Jasper Van der Lugt[5], Esther Hulleman[5,6], Carlos de Andrea[7,8], Itziar Astigarraga[9], Miguel García-Ariza[10], Blanca Lopez-Ibor[11], Maria Villalba[7,12], Frederick F Lang[13], Juan Fueyo[14,15], Candelaria Gomez-Manzano[14,16], Jessica Dobbs[17], Ricardo Diez-Valle[18], Marta M Alonso[1,2], and Sonia Tejada[18]; [1]Program in Solid Tumors, Foundation for the Applied Medical Research, Pamplona, Spain, [2]Department of Pediatrics, Clínica Universidad de Navarra, Pamplona, Spain, [3]Department of Neurology, Clínica Universidad de Navarra, Pamplona, Spain, [4]Division of Molecular Pathology, Institute of Cancer Research, London, UK, [5]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, [6]Department of Pediatric Oncology/Hematology, Cancer Center Amsterdam, Amsterdam University Medical Centers, Amsterdam, Netherlands, [7]Department of Pathology, Clínica Universidad de Navarra, Pamplona, Spain, [8]Health Research Institute of Navarra (IdiSNA), Pamplona, Spain, [9]Department of Pediatrics, Hospital Universitario Cruces, IIS Biocruces-Bizkaia, UPV/EHU, Barakaldo, Spain, [10]Department of Pediatric Oncology, Hospital Cruces, Bilbao, Spain, [11]Department of Pediatric Hematology and Oncology, HM Montepríncipe Hospital, Boadilla del Monte, Spain, [12]Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain, [13]Department of Neurosurgery and Brain Tumor Center, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [14]Department of Genetics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [15]Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [16]Department of NeuroOncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, Houston, TX, USA, [17]DNAtrix, Houston, TX, USA, [18]Department of Neurosurgery, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

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

Susan Chi[1], Antony Hsieh[2], Megan Foley[2], Hongliang Shi[2], Preethi Swamy[2], Jill Rodstrom[2], and Marc Rudoltz[3]; [1]Dana-Farber Cancer Institute, Boston, MA, USA, [2]Blueprint Medicines Corporation, Cambridge, MA, USA, [3]MSR Healthcare Consultants LLC, West Orange, NJ, USA

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

Jonas Ecker[1,2], Florian Selt[1,2], Andrey Korshunov[3,4], David Capper[5], Nicola Dikow[6], Steffen Hirsch[1,6], Christian Sutter[6], Cornelis van Tilburg[1,2], Andreas von Deimling[3,4], David T. W. Jones[1,7], Stefan M. Pfister[1,8], Felix Sahm[3,4], Olaf Witt[1,2], Till Milde[1,2]; [1]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany, [2]Clinical Cooperation Unit Pediatric Oncology, German Cancer Research Center (DKFZ) and German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany, [3]Department of Neuropathology, Heidelberg University Hospital, Heidelberg, Germany, [4]Clinical Cooperation Unit Neuropathology, German Cancer Research Center (DKFZ) and German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany, [5]Department of Neuropathology, Charité – Universitätsmedizin Berlin, Campus Charité Mitte, and German Consortium for Translational Cancer Research (DKTK), Berlin, Germany, [6]Department of Human Genetics, Institute of Human Genetics, Heidelberg University Hospital, Heidelberg, Germany, [7]Pediatric Glioma Research, German Cancer Research Center (DKFZ) and German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany, [8]Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany

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