EPCT-06. A PHASE I STUDY OF MULTI-TARGETED THERAPY IN NEWLY DIAGNOSED OR PROGRESSIVE DIFFUSE INTRINSIC PONTINE GLIOMA

Muhammad Baig, Jason Johnson, Sumit Gupta, Zsila Sadighi, Wafik Zaky, and Soumen Khatua; MD Anderson Cancer Center, Houston, TX, USA

BACKGROUND: Diffuse intrinsic pontine glioma (DIPG) constitutes 80% of pediatric brain stem tumors with a median survival of 12 months. The PI3K/AKT/mTOR pathway is a key oncogenic driver of this tumor. Targeting the chromatin dysregulation through HDAC inhibition, demonstrated benefit in vivo and vitro studies. We completed the first study as a multi-targeted therapy using SAHA and temsirolimus in pediatric DIPG. METHODS: After receiving institutional IRB approval, we enrolled 6 patients on this phase I study using a 3 + 3 statistical design. Patients were divided into stratum 1 and stratum 2, based on newly diagnosed or relapsed DIPG respectively. Stratum I patients received radiation therapy concurrently with vorinostat, followed by maintenance therapy with vorinostat and temsirolimus for 10 cycles (28 day cycle), while in stratum II patients received vorinostat and temsirolimus for 12 cycles. Neuroimaging including diffusion tensor imaging were evaluated where feasible. RESULTS: Three patients were enrolled in each of the stratum. One patient in stratum 1 completed therapy, 2 other demonstrated progressive disease (PD) after 4th and 1st cycle of maintenance therapy respectively. In stratum 2 all patients progressed 2 months after the start of therapy. However no dose-limiting toxicity (DLT) was noted. The patient in stratum 1 who completed therapy, remained free of PD 21 months after diagnosis with continued improvements in the volume of enhancing and T2 hyperintense disease. CONCLUSION: Although no significant benefit was seen as compared to historical controls during this study, no dose limiting toxicity was noticed with this treatment.

EPCT-07. DEBIO1347, AN ORAL FGFR INHIBITOR: RESULTS FROM A SINGLE CENTER STUDY IN RECURRENT/REFRACTORY FGFR ALTERED PEDIATRIC GLIOMAS

Sameer Farouk Sait, Stephen Gilheeney, Ira Dunkel, and Matthias Karajannis; Memorial Sloan Kettering Cancer Center, New York, NY, USA

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 preliminary clinical activity in an adult phase 1 study. METHODS: Five children with progressive/refractory CNS tumors harboring an FGFR gene alteration following prior chemotherapy were treated with Debio1347 at Memorial Sloan Kettering Cancer Center on single patient use protocols. Patients were treated using the 20 mg tablet formulation at the adult recommended phase 2 dose (80 mg/1.73 m2 * BSA once daily). Toxicities were graded using CTCAEv5.0 and imaging response assessments were performed every 8–12 weeks. RESULTS: All AEs were grade 1–2. Most common treatment-related adverse events were ALT increased, hypoalbuminemia and hyperphosphatemia (4 patients). Two patients met criteria for partial response and two patients had stable disease. A 13 month-old patient with a spinal cord high-grade glioma harboring two FGFR1 mutations (V592M, K687) had tumor reduction of 91.7% maintained for 12 months. A 26-month-old patient with a pilomyxoid astrocytoma harboring an FGFR1-TACC1 fusion had a tumor reduction of 74.5% maintained for 9 months. Prolonged disease stabilization was noted in an eight year-old patient with metastatic suprasellar pilomyxoid astrocytoma harboring an FGFR1 mutation (9 months) and in a 14 year-old patient with posterior fossa glioneuronal tumor harboring an FGFR3-TACC3 fusion (18 months and ongoing). CONCLUSIONS: Debio1347 demonstrated tolerable toxicity and promising anti-tumor efficacy in pediatric patients with refractory FGFR altered gliomas. Further studies in this population are warranted.

EPCT-08. ACTIVITY OF LAROTRECTINIB IN PEDIATRIC TROPOMYOSIN RECEPTOR KINASE (TRK) FUSION CANCER PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM (CNS) TUMORS

Hiroaki Goto[1], Birgit Geoerger[2], Steven G. DuBois[3], Juneko E. Grilley-Olson[4], Cornelis M. van Tilburg[5], Johannes Schulte[6], Hyoung Jin Kang[7], Makoto Tahara[8], Valentina Boni[9], Sebastien Perreault[10], Michael Capra[11], John A. Reeves[12], Nicoletta Brega[12], Barrett H. Childs[12], Theodore W. Laetsch[12], David S. Ziegler[12], and François Doz[12]; [1]Kanagawa Children's Medical Center, Yokohama, Japan, [2]Gustave Roussy, Department of Pediatric and Adolescent Oncology, Université Paris-Sud, Université Paris-Saclay, Villejuif, France, [3]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA, [4]Lineberger Cancer Center, University of North Carolina Hospitals, Chapel Hill, NC, USA, [5]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany, [6]Charité – Universitätsmedizin Berlin, Berlin, Germany, [7]Seoul National University Hospital, Seoul, Republic of Korea, [8]National Cancer Center Hospital East, Kashiwa, Japan, [9]START Madrid CIOCC, Madrid, Spain, [10]CHU Sainte Justine, Montreal, Canada, [11]Our Lady Children's Hospital, Dublin, Ireland, [12]Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA

BACKGROUND: TRK fusions are oncogenic drivers in a variety of tumors, many involving the CNS. Larotrectinib, a selective FDA- and EMA-approved TRK inhibitor, demonstrated a 79% objective response rate (ORR) and a 35.2-month median duration of response (DoR) in adult and pediatric patients with various non-CNS solid tumors harboring *NTRK* gene fusions. We report the clinical activity of larotrectinib in pediatric patients with primary TRK fusion CNS tumors. METHODS: Patients aged <18 years with primary CNS tumors harboring an *NTRK* gene fusion detected by local molecular testing who were treated with larotrectinib in two clinical trials (NCT02637687, NCT02576431) were identified. Larotrectinib was administered until disease progression, withdrawal, or unacceptable toxicity. Disease status was investigator assessed (RANO). RESULTS: As of February 2019, 14 pediatric patients with primary TRK fusion CNS tumors were identified. Gene fusions involved *NTRK2* (n=10), *NTRK1* (n=2), and *NTRK3* (n=2). Median age was 7.0 years (range 1.3–16.7). ORR was 45% (95% CI 17–77%) among 11 evaluable patients. Two patients had complete responses (pending confirmation), three had confirmed partial responses, and six had stable disease. 24-week disease control rate was 73%. DoR ranged from 2.6+ to 5.5+ months and progression-free survival ranged from 0.03+ to 13.9+ months. Duration of treatment ranged from 0.03+ to 16.6+ months. Treatment-emergent adverse events were mainly grade 1–2. CONCLUSIONS: Larotrectinib resulted in objective responses and durable disease control in pediatric patients with primary TRK fusion CNS tumors. These results support expanded testing for *NTRK* gene fusions in patients with CNS tumors.

EPCT-09. CLR 131 IN PATIENTS WITH RELAPSED OR REFRACTORY PEDIATRIC MALIGNANCIES

Diane Puccetti[1], Mario Otto[1], Daniel Morgenstern[2], Kenneth DeSantes[1], Steven Cho[3,4], Lance Hall[5], Kate Oliver[6], and Jarrod Longcor[6]; [1]University of Wisconsin American Family Children's Hospital, Madison, WI, USA, [2]Hospital for Sick Children, Toronto, ON, Canada, [3]University of Wisconsin-Madison Department of Radiology, Madison, WI, USA, [4]University of Wisconsin Carbone Cancer Center, Madison, WI, USA, [5]Emory University Department of Radiology and Imaging Sciences, Atlanta, GA, USA, [6]Cellectar Biosciences, Florham Park, NJ, USA

BACKGROUND: CLR 131 is a novel targeted radiotherapeutic that exploits the selective uptake and retention of phospholipid ethers by malignant cells. CLR 131 selectively delivers radiation to malignant tumor cells, thus minimizing radiation exposure to normal tissues. OBJECTIVE: CLR 131 is being examined in a Phase 1 trial, CLOVER-2 (NCT03478462), to determine the safety, tolerability, and initial efficacy of CLR 131 in children and adolescents with relapsed/refractory malignancies. METHODS: Eligibility criteria include children with relapsed or refractory solid tumors or malignant brain tumors for which there are no standard treatment options with curative potential. Subjects must be between ages 2 and 21 with no limit to the number of prior therapies. CLR 131 is administered as a single infusion in escalating doses beginning at 15 mCi/m^2. Adverse events (AEs) are graded by NCI-CTCAE v5. RESULTS: As of 10Jan2020, four subjects with brain tumors have received CLR 131; one at 15 mCi/m^2 and three at 30 mCi/m^2. Diagnoses included DIPG (2), glioblastoma (1), and medulloblastoma (1). Median age is 13 years (range 10–15) and patients received a median of two prior therapies (range 1 to 8). There were no treatment emergent AEs at the 15 mCi/m^2 dose level attributed to CLR 131 by the investigator. Assessment of the 30 mCi/m^2 dose level is ongoing. CONCLUSIONS: CLR 131 is a unique, first in class targeted radiotherapeutic for pediatric malignancies. Preliminary data shows an acceptable and expected safety profile in this patient population. Dose escalation to determine the highest tolerated dose is ongoing.

EPCT-11. PHASE 1 STUDY OF FLUVASTATIN-CELECOXIB COMBINATION IN CHILDREN WITH RELAPSING/REFRACTORY OPTICO-CHIASMATIC LOW-GRADE GLIOMA OR HIGH-GRADE GLIOMAS (FLUVABREX): FINAL RESULTS

Nicolas Andrew[1], Arthur Sterin[1], Caroline Solas[1], Marie-Cécile Le Deley[2], Alicia Probst[2], Isabelle Aerts[3], Cécile Faure-Conter[4], Anne-Isabelle Bertozzi[5], Pascal Chastagner[6], Natacha Entz-Werle[7], Emilie De Carli[8], Philippe Dory-Lautrec[1], Gauthier Bouche[9], and Pierre Leblond[2,4]; [1]CHU La Timone, Marseille, France. [2]Centre Oscar Lambret, Lille, France. [3]Institut Curie, Paris, France. [4]IHOPE, Lyon, France. [5]CHU Purpan, Toulouse, France. [6]CHU Brabois, Nancy, France. [7]CHU Hautepierre, Stasbourg, France. [8]CHU Angers, Angers, France. [9]AntiCancer Fund, Strombeek-Bever, Belgium

BACKGROUND: Preclinical data support the activity of celecoxib and fluvastatin in high grade (HGG) and low grade gliomas (LGG). A Phase I study was designed to evaluate this combination in children with re-

fractory/relapsed glioma. AIM: To assess the safety, pharmacokinetics (PK), maximum tolerated dose, Recommended Dose for Phase II (RDP2). METHOD: Multicenter phase I trial, including patients aged 6 to 21 year old. Fluvastatin starting dose was 2 mg/kg/day, 14/28 days, with fixed dose of celecoxib (200–800 mg /day). Four dose levels of fluvastatin (2, 4, 6, 8 mg/kg/day) were evaluated. A Continual Reassessment Method was used for dose escalation. Dose-limiting toxicities (DLT) were determined on the 1st cycle. PK samples were obtained at D1 and D14 of cycle 1, pre-dose of cycle 2. RESULTS: 20 patients were enrolled with a median age of 12 years (5.9–19). They previously received a median of 3 (1–7) lines of treatment. Ten patients were treated for LGG and 10 for HGG, receiving a median of 3.5 cycles (1–21). Patients with LGG received a median of 9 cycles (1–21). Among the 17 patients evaluable for DLT, 2 DLTs were reported: 1 grade 3 maculo-papular rash (4 mg/kg), and 1 grade 4 increase of CPK (6 mg/kg). The RP2D of fluvastatin is 6 mg/kg/day. CONCLUSION: In children with refractory/relapsed glioma, the RDP2 of fluvastatin associated with celecoxib is 6 mg/kg/day. This combination is well tolerated encouraging a phase 2 study in LGG.

EPCT-12. PNOC015: PHASE 1 STUDY OF MTX110 (AQUEOUS PANOBINOSTAT) DELIVERED BY CONVECTION ENHANCED DELIVERY (CED) IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) PREVIOUSLY TREATED WITH RADIATION THERAPY

Sabine Mueller[1], Cassie Kline[1], Javier Villanueva-Meyer[1], Carly Hoffman[1], Shannon Raber[1], Erin Bonner[2], Javad Nazarian[3], Shannon Lundy[1], Annette M. Molinaro[1], Michael Prados[1], Mariella Filbin[4], and Nalin Gupta[1]; [1]University of California, San Francisco, San Francisco, CA, USA, [2]Children's National Medical Center, Washington, DC, USA, [3]Children's Hospital Zurich - Eleonore Foundation, Zurich, Switzerland, [4]Dana-Farber Cancer Institute, Boston, MA, USA

OBJECTIVE: To determine safety and distribution of MTX110 delivered by CED in newly diagnosed DIPG patients. METHODS: DIPG patients (3–21 years) were enrolled after radiation. CED of MTX110 combined with gadoteridol was completed based on dose levels (DL) (30–90 µM with volumes ranging from 3 cc (single dose) to 2 consecutive doses of 6 cc; total number of DL=7). Catheter position was chosen to maximize tumor coverage. Distribution of infusate was monitored with real-time MR imaging. Repeat CED was performed every 4–8 weeks if tolerated. Quality of life (QOL) assessments using PedsQL Generic Core and Brain Tumor modules were obtained at baseline (n=5), 3-months (n=3), and end of therapy (n=2). Single-cell RNA sequencing and analysis of histone modifications was performed to assess pharmacodynamic effects on DIPG cells. RESULTS: Between May 2018-Dec 2019, 6 patients were enrolled (median age 8 years, range 5–21). Dose limiting toxicities included: grade 3 gait disturbance (DL7; cycle 1); grade 3 muscle weakness/vagus nerve disorder (DL5; cycle 4) and grade 2 intolerable dysphagia (DL7; cycle 4). Twelve CED procedures were completed at DL7 and repeated cycles ranged from 2 to 7. Infusion to distribution volume ratio was approximately 1:3.5. There were no significant changes in self-reported QOL. Parent ratings of patients' worry ($p = 0.04$) and overall QOL ($p = 0.03$) significantly decreased at 3-months. CONCLUSION: Repeat CED of MTX110 at the highest dose is tolerable. Tissue concentrations are likely to be substantially higher compared to oral dosing. Pharmacodynamic effects will be presented.

EPCT-13. CMV PP65 RNA-PULSED DENDRITIC CELL VACCINES FOR PEDIATRIC GLIOBLASTOMA AND MEDULLOBLASTOMA: PHASE I TRIAL RESULTS

Daniel Landi[1,2], Gary Archer[2], Timothy Driscoll[1], Eric Lipp[2], Bridget Archambault[1], Eric Thompson[2,3], Charlene Flahiff[2], Denise Jaggers[2], Kathleen Hahn[2], Patrick Healy[4], Luis Ramirez[4], James Herndon[4], Kristin Schroeder[1,2], John Sampson[2], and David Ashley[1,2]; [1]Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA, [2]Preston Robert Tisch Brain Tumor Center, Duke University, Durham, NC, USA, [3]Department of Neurosurgery, Duke University, Durham, NC, USA, [4]Duke Cancer Institute Biostatistics, Duke University, Durham, NC, USA

BACKGROUND: Recurrent medulloblastoma and malignant glioma are lethal tumors that are virtually incurable. The cytomegalovirus (CMV) antigen pp65 is ubiquitously expressed on medulloblastoma and malignant glioma but not on healthy brain. We evaluated autologous CMV pp65 RNA-pulsed dendritic cell (DC) vaccines in children and young adults in a phase I trial. METHODS: Circulating monocytes were harvested using leukapheresis, differentiated into DCs, matured, and pulsed with pp65 RNA using electroporation. DCs were packaged into vaccines ($2x10^7$DC/vaccine) and administered intradermally following tetanus-diphtheria toxoid site preconditioning every 2 weeks x3, then monthly. The primary objectives of the study were to establish the feasibility of generating at least 3 vaccines and safety. An exploratory objective was to evaluate the ability of vaccination to create and enhance patient pp65-specific T cell responses. RESULTS: Eleven patients were enrolled with medulloblastoma (n=3) or glioblastoma (n=8). Ages ranged from 9–30 years old (mean 15.5y). Ten of 11 patients (91%) generated at least 3 vaccines (mean 6.2). Eight patients received at least 3 vaccines. To date, 4 patients have received all generated vaccines without progression, 4 patients have progressed, and 2 patients are still receiving vaccines. There have not been any severe adverse events probably or definitely related to vaccines. More mature data will be presented at ISPNO. CONCLUSIONS: Leukapheresis and monocyte differentiation is a feasible strategy for generating adequate DCs for active immunization in children with malignant brain tumors. CMV pp65 RNA-pulsed DCs are well-tolerated and immunogenic. Efficacy endpoints will be evaluated in a subsequent phase II trial.

EPCT-15. THE REMIND TRIAL: MULTI-ANTIGEN TARGETED T CELLS FOR PEDIATRIC CNS TUMORS

Melanie Grant[1], Maria Fernanda Fortiz[1], Lu Wang[1], Haili Lang[1], Anushree Datar[1], Emily Reynolds[1], Madeline Terpilowski[1], Chris Lazarski[1], Jay Tanna[1], Adriana Pitino[1], Nan Zhang[1], Fahmida Hoq[1], Patrick Hanley[1], Lindsay Kilburn[1], Roger Packer[1,2], Brian Rood[1], Catherine Bollard[1,2], and Eugene Hwang[1]; [1]Children's National Hospital, Washington, DC, USA, [2]George Washington University, Washington, DC, USA

BACKGROUND: Patients with relapsed CNS malignancies or DIPG face terrible prognoses. We hypothesized that T cells specific for 3 tumor-associated antigens (TAA), WT1, PRAME and survivin, would be safe and elicit anti-tumor immunity. METHODS: Patients (n=9) have received autologous tumor antigen-associated T cells (TAAT) (up to $4x10^7/m^2$) for newly diagnosed DIPG (Group A) or recurrent CNS malignancies (Group B) on a Phase I dose-escalation study (NCT03652545) and were monitored for safety and response. RESULTS/DISCUSSION: 9/9 patients who received TAAT completed the 45-day safety monitoring phase with no dose-limiting toxicities. Infused cells were predominantly CD3+ T cells (median 96%; range: 87–99%), with CD4+ and CD8+ comprising 16% (range: 5–87%) and 40% (range: 4–67%) of the CD3+ cells, respectively. TAAT with specificity for 1–3 TAAs, at varying frequencies, was demonstrated in 8/9 TAAT by anti-IFN-γ ELISPOT. Plasma cytokine profiles demonstrated infusion-related immune cytokine responses. In summary, TAAT are safe and may elicit anti-tumor responses in vivo. To confirm TAAT-driven effects, we are evaluating plasma proteomic profiles for immune-response signatures and assessing unique T cell receptor rearrangements of infused TAAT. Response assessment and dose escalation are ongoing.

EPCT-16. A PHASE IB STUDY OF PTC596 IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA AND HIGH GRADE GLIOMA

Natasha Pillay Smiley[1], Patricia Baxter[2], Shiva Kumar[1], Eugene Hwang[3], John Breneman[4], Adam Lane[1], Renee Doughman[5], Michelle Deutsch[1], Charles Stevenson[5], Clinton Stewart[6], Jim Leach[7], Xiao-Nan Li[8], Sonia Romero[9], Pius Maliakal[10], Lan Gao[10], Maryam Fouladi[5], and Rachid Drissi[5]; [1]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA, [2]Texas Children's Hospital, Houston, TX, USA, [3]Children's National Hospital, Washington, District of Columbia, USA, [4]University of Cincinnati, Cincinnati, OH, USA, [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [6]St. Jude Children's Hospital, Memphis, TN, USA, [7]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [8]Ann & Robert H, Lurie Children's Hospital, Chicago, IL, USA, [9]PTC Therapeutics, South Plainfield, NJ, USA, [10]PTC Therapeutics, Plainfield, NJ, USA

BACKGROUND: BMI-1 is highly expressed in DIPG. Downregulation leads to inhibition of cell proliferation, cell cycle signaling, self-renewal, telomerase expression, activity, and suppression of DIPG cell migration. Targeted inhibition of BMI-1 sensitizes DIPG cells to radiation and drug-induced DNA damage. PTC596 (formulated by PTC Therapeutics, Inc.) is a novel, orally available drug that inhibits microtubule polymerization, resulting in G2/M cell cycle arrest and post-translational modification of BMI-1 protein and reduced BMI-1 protein levels. OBJECTIVES: To estimate the maximum tolerated dose and describe dose limiting toxicities, pharmacokinetics and pharmacodynamics of PTC596 in children 3–21 years of age with newly diagnosed diffuse intrinsic pontine glioma and high-grade gliomas. METHODS: PTC596 is administered twice per week orally during radiotherapy and as maintenance for up to two years. The starting dose of PTC596 was 200 mg/m^2, with a subsequent dose level of $260mg/m^2$/dose. Pharmacokinetics are performed in Cycles 1 and 2. RESULTS: This study is currently ongoing. Nine patients (7 with DIPG, 2 with HGG), 8 evaluable, have been enrolled. At dose level 1, 200 mg/m^2, three evaluable patients were enrolled and experienced no DLTs. At dose level 2, among 5 evaluable patients, 2 experienced dose-limiting grade 4 neutropenia. PTC596 has been otherwise well tolerated. Five patients remain in Cycles 2–11. CONCLUSION: This phase I trial is ongoing. PTC596 is tolerable at dose level 1. We