DIPG-80. CLINICAL AND RADIOGRAPHIC RESPONSE TO ONC201 IN A PATIENT WITH A THALAMIC H3K27M AND BRAFV600E MUTANT DIFFUSE MIDLINE HIGH GRADE GLOMA
Elizabeth Duke1, Jonathan Murrack1, Rohinton Vakil2, Joshua Allen2, and Lindsay Kozlowska2
1Children’s National Hospital, Washington, DC, USA, 2Oncoceleus, Inc, Philadelphia, PA, USA

Recent improved understanding of the molecular markers of high grade gliomas has led to the development of drugs aimed at molecular targets. One of the most promising drugs is ONC201, a BRAFV600E antagonist that induces apoptosis and repressing uncontrolled cellular division. This patient presented with a BRAFV600E mutant high grade glioma with concomitant H3K27M mutation. The patient received Onco201 as a second line therapy after standard-line treatment with lomustine and procarbazine. The patient showed initial response to therapy with reduced gadolinium enhancement and contralateral mass effect. At the time of progression, the patient received a novel agent, and the patient was able to obtain a second line response to therapy. The patient was able to achieve a clinically meaningful response with ONC201 and was able to maintain it for the duration of therapy. The patient eventually progressed on therapy.

DIPG-82. CLINICAL EXPERIENCE OF CONVECTION ENHANCED DELIVERY (CED) OF CARBOPlatin AND SOlID VAloproACE (CPSVA) INTO THE PONS FOR THE TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) IN CHILDREN AND YOUNG ADULTS AFTER RADIOTHERAPY
Elwira Michniewicz1,2, Peter Collins3, Harpreet Hyare4,5, Anamir Shankar4,6, Alison Buenemann1, Milo Hollingworth7, and Steven Gill8; 1The Royal Marsden Hospital, Sutton, United Kingdom, 2Harley Street Children’s Hospital, London, United Kingdom, 3University of Nottingham, Nottingham, United Kingdom, 4University College London Hospitals NHS Foundation Trust, London, United Kingdom, 5University of Bristol, Bristol, United Kingdom

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 intramedullary CED of carboplatin and sodium valproate to the pons through the Renshaw Drug Delivery System (RDDs). METHODS: Retrospective review (2017-2020) of children with DIPG, who following radiotherapy received compassionate treatment with CED of carboplatin and sodium valproate (median survival 7 months). RESULTS: 13 children 3–19 years (mean 6.9 years) were included. Median progression free survival (PFS) and 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)
Filip Michniewicz1,2, Federica Saletta1, Jourdin Rouen1,2, David Ziegler1,2, and Orazio Vittorio1,2; 1Children’s Cancer Institute, Lowy Cancer Research Centre, Sydney, NSW, Australia, 2UNSW School of Women’s and Children’s Health, Sydney, NSW, Australia

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 have shown in vitro and in vivo 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.

Cytotoxic 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 treated with TEPA and copper concentrations. Immunofluorescence and TEPA treatment demonstrated reduced phosphorylation of AKT, ERK5 and STAT3. Conversely, Western blot analysis of DIPG cell lines treated with a phosphomimetic expression of AKT, ERK1/2, ERK5 and STAT3. These 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. The study documents the role of RTK-mediated signaling promoting DIPG proliferation. This implies that reducing copper with clinically available chelators can represent a potential anti-cancer treatment for DIPG.

DIPG-84. COMPLEMENTARY AND ALTERNATIVE MEDICINE IN DIFFUSE INTRINSIC PONTINE GLOMA
Fatemeh Khodavand,1 Adil Hayat,2 Hendrikse4,5, and Gertjan Kaspers1,2
1Christoph Kramm,2 Sophie Veldhuijzen van Zanten1,2, and Dannis van Vuurden1; 1Amsterdam UMC - location VUmc, Amsterdam, Netherlands, 2Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands, 3University medical center Goettingen, Goettingen, Germany

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 treatment of illness. RESULTS: 120 parents and 7 physicians contributed to the online survey between January and May 2020. Physicians estimated that ≤40% of their patients used CAM, whereas ≥60% of the parents reported to have used CAM to treat their child during time of illness. CAM use 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 (p = 0.014) to significant difference was found between CAM users and non-users based on ethnicity (p = 0.014). 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**

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

Karen Wright1, Emily Krywka1, Lianne Greempan1, Susan Chi2, Kee Ikat Yeo1, Sabine Mueller2, Michael Prado2, and Daphne Haas-Kogan1,2,1

**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/m². Dose limiting toxicities were determined after one cycle. RESULTS: We treated nine eligible patients at 280, 350, and 420 mg/m². Eight patients had KIAA1549/BRAF fusions. One patient with NFI did not have a biopsy. None of the patients experienced DLTs. All patients 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 responses. DAY101 was well-tolerated with 1 hypoalbuminemia. PK data will be available.

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

Holly Linsalata1, Arzu Onar-Thomas2, Mchnet Kocak3, Tonya Young Poussaint4, Grish Dhall5, Alberto Broniscer6, Anna Vinitsky7, Tobey MacDonald8, Osvd Tifran9, Jason Fangusaro10, and Ira Dunkel11,12,13

1Department of Pediatrics, Texas Children’s Hospital/Baylor College of Medicine, Houston, TX, USA, 2Department of Biostatistics, St Jude Children’s Hospital, Memphis, TN, USA, 3Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA, 4Department of Radiology, Boston Children’s Hospital, Boston, MA, USA, 5Division of Hematology and Oncology, Children’s of Alabama, Birmingham, AL, USA, 6Children’s Hospital of Pittsburgh, Pittsburgh, PA, USA, 7Division of Neuro-Oncology, St. Jude Children’s Research Hospital, Memphis, TN, USA, 8Children’s Healthcare of Atlanta and Emory University, Atlanta, GA, USA, 9Apexigen, Inc., San Carlos, CA, USA, 10Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

**BACKGROUND:** CD40 is a co-stimulatory molecule expressed on antigen presenting cells (APCs). APX005M is a CD40 agonistic 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 investigational phase 1 study to evaluate the safety and tolerability of APX005M in pediatric subjects with recurrent/refractory brain tumors. METHODS: Twenty eligible patients were enrolled on this study. Two dose levels of APX005M were evaluated in adults (8 and 14 mg/kg). In children, a dose of 14 mg/kg was selected as the MTD. CONCLUSION: APX005M is safe and well-tolerated in children with recurrent/refractory brain tumors, and a phase 2 study is planned.

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

Derek Hanson1, Hackensack University Medical Center, Hackensack, NJ, USA, 2University of Florida, Gainesville, FL, USA, 3Seattle Children’s Hospital, Seattle, WA, USA, 4Ann and Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, USA, 5Children’s Hospital of Pittsburgh, Pittsburgh, PA, USA, 6Children’s Healthcare of Atlanta and Emory University, Atlanta, GA, USA, 7Apexigen, Inc., San Carlos, CA, USA, 8Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

**BACKGROUND:** 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 agent Hwanga 2-OHOA in a host of animal models. A European phase I/II 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 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 1a followed by 1b and planned to assess the safety of cohort 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.

**EPTC-04. A PHASE I TRIAL OF THE CDK 4/6 INHIBITOR PALBOCICLIB IN PEDIATRIC PATIENTS WITH PROGRESSIVE OR RECURRENT CNS TUMORS: A PEDIATRIC BRAIN TUMOR CONSORTIUM (PBTC) STUDY**

David Van Mater1, Sridharan Gururangan2, Sarah Leary3, Oren Becher4, Joanna Phillips5, Je Huang6, Olivia Campagne7, Tina Poussant8, Stewart Goldman9, Patricia Baxter10, Grish Dhall11, Giles Robinson12, Marieke DeWiere-Schottmiller13, Arzu Onar-Thomas14, Ira Dunkel15,16,17 and Maryam Fouladi18,19,20

1Duke University Medical Center, Durham, NC, USA, 2University of Florida, Gainesville, FL, USA, 3Seattle Children’s Hospital, Seattle, WA, USA, 4Ann and Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, USA, 5Children’s Hospital of Pittsburgh, Pittsburgh, PA, USA, 6Children’s Healthcare of Atlanta and Emory University, Atlanta, GA, USA, 7Apexigen, Inc., San Carlos, CA, USA, 8Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA, 9Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

**BACKGROUND:** 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 phase 1A data provide initial pharmacokinetic parameters to describe oral weekly palbociclib in pediatric patients with radiographic persistent/recurrent/progressive LGA. 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.