### RARE-32. PHASE 0 AND FEASIBILITY SINGLE-INSTITUTION CLINICAL TRIAL OF INTRAVENOUS TOCILIZUMAB FOR ADAMANTINOMATOUS CRANIOPHARYNGIOMA

Kathleen Dorris[1], Ashley Mettetal[2], Nathan Dahl[1], Molly Hemenway[1], Shelby Winzent-Oonk[1], Eric Prince[1], Trinka Vijmasi[1], Jennifer McWilliams[1], Kimberly Jordan[1], David Mirsky[1], Lindsey Hoffman[3], Todd Hankinson[1]; [1]University of Colorado, Aurora, CO, USA. [2]Children's Hospital Colorado, Aurora, CO, USA. [3]Phoenix Children's Hospital, Phoenix, AZ, USA

BACKGROUND: Adamantinomatous craniopharyngioma (ACP) is a devastating skull-base tumor believed to derive from epithelial remnants of the primordial craniopharyngeal duct (Rathke's pouch), which gives rise to the anterior pituitary gland. ACP lacks medical antitumor therapies. Current standard therapy with surgery and radiation is associated with poor quality of life. Clinical and preclinical data indicate that IL-6 blockade may contribute to ACP tumor control. METHODS: Children aged 2–21 years with newly diagnosed or previously treated ACP with measurable disease are eligible for the Phase 0/feasibility single-institution clinical trial (NCT03970226) of intravenous (IV) tocilizumab at Children's Hospital Colorado. The phase I stratum involves IV tocilizumab prior to a standard-of-care surgical resection. The feasibility portion of the trial involves IV tocilizumab every two weeks for up to 13 28-day cycles. Tocilizumab is administered at the established weight-based pediatric dosage of 8 mg/kg for patients who weigh ≥30kg or 12 mg/kg for patients who weigh <30kg. RESULTS: To date, three patients have been enrolled on the Phase 0 component of the trial. These patients demonstrated clinically relevant levels of tocilizumab (≥ 4μg/mL) in serum, cyst fluid, and/or tumor tissue, compared to undetectable levels in control samples. Two patients (1 male and 1 female; median age 10.5 years) have enrolled on the feasibility stratum; one patient had best response of minor response but met definition of progressive disease at cycle 11. One patient with extensive disease required dose reduction for myelosuppression. CONCLUSION: Systemic delivery of tocilizumab at the established pediatric dosage is promising for treatment of ACP based on preclinical work and its demonstrated penetration into cystic and solid portions of ACP tumors. The therapy to date has been well tolerated overall. Further study is planned through a CONNECT consortium international Phase II trial.

## DIFFUSE MIDLINE GLIOMA/DIPG

### DIPG-01. TARGETING P300: A MASTER REGULATOR OF CHILDHOOD DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

Pinki Chowdhury[1,2], Robert Lober[1,2]; [1]Dayton Children's Hospital, Dayton, Ohio, USA. [2]Wright State University Boonshoft School of Medicine, Dayton, Ohio, USA

Diffuse intrinsic pontine gliomas (DIPG) are heterogeneous, highly aggressive, accounting for ~10% of all childhood central nervous system tumors that are poorly understood. The heterogeneity of the cell populations could contribute to major variability in tumor growth and chemoresistance followed by inadequate treatment responses. Approximately 80% of DIPG patients harbor mutations on lysine-27 of histone-3 (H3K27M), which forms heterotypic nucleosomes with normal, acetylated-H3K27 (H3K27ac), and colocalizes with bromodomain proteins to sites of active transcription. p300 (or EP300) bromodomain has recently been exploited as a potential therapeutic target in other cancer, with a small molecule inhibitor showing antiproliferative activity. Bromodomain inhibitors (BrDi) have been suggested as a potential therapeutic target for DIPG too which showed antiproliferative activity *in vitro*. *We therefore hypothesize that p300 bromodomain inhibition is a potential therapeutic strategy that must be urgently explored in DIPG*. p300 is a multi-domain enhancer protein, expressed in 80% of gliomas, responsible for H3K27ac mark and localizes to sites of H3K27ac enrichment, where it serves as an essential binding partner of histones to various transcription factors. p300 interacts with BMI-1, a polycomb repressive complex 1 (PRC1) group of transcription factor, through an intermediate protein NANOG, which promotes cell proliferation in head-neck squamous cell carcinoma. However, immunohistochemical study demonstrated that there is no NANOG expression found in DIPG patient samples. Therefore, *we propose that p300 and BMI-1 interact with each other directly or through an intermediate molecule, essential for tumor growth and thus can be considered as a possible therapeutic target for DIPG*. The overall outcome of this research will reveal the unexplored mechanisms of DIPG cell proliferation to overcome chemoresistance in sick children and develop drug/combination against this deadly malignancy, which can be used for future clinical trials.

### DIPG-02. ROLE OF A BEVACIZUMAB-BASED REGIME IN THE TREATMENT OF CHILDREN WITH DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG): A SYSTEMATIC REVIEW

Mia Evans, Ria Gill, Kim Bull; University of Southampton, Southampton, United Kingdom

BACKGROUND: Diffuse intrinsic pontine glioma (DIPG) is an aggressive paediatric brainstem tumour. There are no effective treatments and median survival is 11.2 months, therefore maintaining quality of life (QOL) is a priority for many families. Bevacizumab, an anti-VEGF IgG antibody, has the potential to improve QOL and survival in DIPG, but has never been evaluated systematically. AIM: To collate the evidence and assess the role of this drug, in the treatment of DIPG. METHODS: MEDLINE, EMBASE, Scopus and Web of Science were searched for relevant studies using terms developed from PICO criteria, including alternatives for Bevacizumab and DIPG. One reviewer screened titles and abstracts, then two reviewers screened full texts. Data were extracted into tables and study quality assessed using MINORS and JBI tools. RESULTS: Searching revealed 1,001 papers; after deduplication 851 remained. After screening of titles and abstracts, 28 full texts were screened, resulting in the inclusion of 11 studies. All studies evaluated more than one outcome. Four studies reported a median overall survival longer than historical data, however, two determined no significant impact. Five studies reported a radiological response in a proportion of participants and two reported no response. Three studies evaluating clinical response, reported improvement in a proportion of patients. Three studies evaluating QOL reported stability or improvement. Four studies evaluating steroid use reported reductions in the proportion of patients receiving steroids. In the treatment of radiation necrosis, Bevacizumab led to clinical improvement in 6/12 patients in 2 studies and permitted a reduction in steroid use in the majority of patients. CONCLUSION: Insufficient evidence means the role of Bevacizumab in the treatment of DIPG is unclear. However, Bevacizumab may be beneficial to some patients. The review highlights the need for further research in this area, particularly randomised controlled trials. More effective therapies are desperately needed.

### DIPG-03. THERAPEUTIC TARGETING OF PURINE BIOSYNTHESIS IN DIPG

Ian Mersich[1,2], Biplab Dasgupta[1,2]; [1]Cincinnati Children's Hospital, Cincinnati, Ohio, USA. [2]University of Cincinnati, Cincinnati, Ohio, USA

Diffuse intrinsic pontine glioma (DIPG) is an incurable brainstem malignancy in children. Little progress has been made in treating this deadly disease due to its inoperable location and treatments aimed at targets defined in adult gliomas. Currently there are no targeted therapies that significantly improve overall survival in patients with this disease. To this end, we are developing a metabolic profile for this disease by integrating metabolomics and gene expression data from cell lines derived from DIPG patient tumors. Our long-term goal is to significantly improve the overall survival of children with DIPG by identifying novel therapeutic targets. Central to this goal is our investigation into dysregulated purine metabolism in these tumors. We've integrated gene expression and metabolomic datasets for DIPG cells and identified a potential therapeutic target in the de novo purine biosynthesis (DNPB) pathway. Genetic knockout experiments confirmed that DIPG cells require the last enzyme in the DNPB pathway, ATIC, for survival. Furthermore, we have identified a compound that disrupts ATIC homo-dimerization, which is required for ATIC catalytic activity. Our preliminary data demonstrates this compound may offer clinical benefits over traditional antifolates that target this same pathway; however, the mechanism leading to selective cytotoxicity was unclear. Antifolates such as methotrexate competitively inhibit folate binding sites in multiple enzymes within this pathway; however, there are known mechanisms of resistance to these drugs. We show that the ATIC dimerization inhibitor differs from the antifolates by disrupting a multi-enzyme complex known as the purinosome, which requires intact, functional ATIC for assembly. Furthermore, targeting ATIC through genetic and pharmacological inhibition in vivo has extended survival in our PDX mouse model of DIPG.

### DIPG-04. FEASIBILITY AND EARLY RESULTS OF PHASE 2 OPEN LABEL RANDOMIZED STUDY OF RADIOTHERAPY(RT), CONCOMITANT NIMOTUZUMAB AND VINORELBINE AND RE-IRRADIATION AT RELAPSE, VERSUS MULTIPLE ELECTIVE RADIOTHERAPY COURSES WITH CONCOMITANT VINORELBINE AND NIMOTUZUMAB FOR NEWLY DIAGNOSED CHILDHOOD AND ADOLESCENCE DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

maura massimino[1], veronica Biassoni[1], Angela Mastronuzzi[2], Elisabetta Schiavello[1], Francesco Barretta[1], Lucia Quaglietta[3], Claudia Milanaccio[4], Emilia Pecori[1], Antonella Cacchione[2], Luna Boschetti[1], Valentina Di Ruscio[2], Silvia Chiesa[5], Giuseppe Scimone[6], Salvina Barra[7], Lucia De Martino[3], Antonia Ramaglia[4], Stefania Picariello[3], Antonio Verrico[4], Ombretta Alessandro[1], Sabina Vennarini[1], Marta Podda[1], Giovanna Gattuso[1], Giuseppe Cinalli[3], Manila Antonelli[8], Piergiorgio Modena[9], Loris De Cecco[1], Francesca R. Buttarelli[8], Lorenza Gandola[1]; [1]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy. [2]Ospedale Pediatrico Bambino Gesù, Roma, Italy. [3]Ospedale Santobono-Pausilipon, Napoli, Italy. [4]Ospedale Pediatrico Giannina Gaslini, Genova, Italy. [5], Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy. [6]Ospedale San Giovanni di Dio e Ruggi D'Aragona, Salerno, Italy. [7]Policlinico S. Martico, Genova, Italy. [8]Università La Sapienza, Roma, Italy. [9]Ospedale S.Anna, Como, Italy

BACKGROUND: The purposes of this trial were to evaluate the feasibility, response, PFS/OS of a randomized study comparing two different