Gaslini, Genoa, Italy. [3]Pharmacy, IRCCS Istituto Giannina Gaslini, Genoa, Genoa, Italy. [4]Neurosurgery Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

BRAF inhibitors (iBRAF) are under investigations in ongoing clinical trials for pediatric brain tumor treatment. Preliminary data regarding the pediatric population report pyrexia, hematological, dermatological, cardiac, and ophthalmic toxicities among the most common adverse events. Acute kidney injury (AKI), mainly due to tubular interstitial injury, has been reported in the adult population. With our study we want to contribute to a more comprehensive knowledge of the short- and long-term nephrological adverse effects of iBRAF in a pediatric population. We collected and reviewed clinical and laboratory data of all patients treated with iBRAF for pediatric central nervous system tumors at our Institution and available for publication. AKI was monitored through serial creatinine measurements, kidney function with estimated glomerular filtration rate (eGFR) and kidney injury with creatinuria/proteinuria ratio. Tubular injury was evaluated with fractional excretion of sodium, potassium and magnesium and with glycosuria. Moreover, urine was examined to detect presence and morphology of erythrocytes. Eight patients were identified, 3 females; median age at treatment start was 9 years (range 2,75 – 18,75). Six patients with BRAFV600E–mutated pediatric Low-Grade Glioma were treated with Vemurafenib, 1 patient with BRAFV600E-mutated pediatric High-Grade Glioma was treated with Vemurafenib and 1 patient with BRAFV600E-mutated Langerhans Cell Histiocytoses was treated with Dabrafenib. Seven patients were considered for analysis. After a median follow up of 3,83 years (range 2,25 – 6,58) no AKI was reported and all patients but two retained normal eGFR at last follow up. No tubular and glomerular injury laboratory findings were detected, and erythrocytes in the urine resulted always below the upper limit of normality. CONCLUSIONS: iBRAF were not associated with AKI and tubular injury. Nevertheless, some data, namely significative decrease of eGFR in two out of seven patients, warrants further investigations.

### LGG-35. DYSLIPIDEMIA IN CHILDREN TREATED WITH BRAF INHIBITORS FOR BRAIN TUMOR, A NEW SIDE EFFECT? A SINGLE CENTER RETROSPECTIVE STUDY

Marco Crocco[1,2], Antonio Verrico[1], Claudia Milanaccio[1], Gianluca Piccolo[1,2], Gabriele Gaggero[3], Patrizia De Marco[4], Valentina Iurilli[5], Sonia Di Profio[6], Maria Grazia Calevo[7], Emilio Casalini[8,2], Natascia Di Iorgi[8,2]; [1]Neuroncology Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy. [2]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, Italy. [3]Department of Clinical Pathology, IRCCS Ospedale Policlinico San Martino, Genova, Italy. [4]UOC Genetica Medica, IRCCS Istituto Giannina Gaslini, Genova, Italy. [5]Pharmacy Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy. [6]Clinical Psychology, IRCCS Istituto Giannina Gaslini, Genova, Italy. [7]Epidemiology and Biostatistics Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy. [8]Department of Pediatrics, IRCCS Istituto Giannina Gaslini, Genova, Italy

The targeted therapies for brain tumors are innovative and promising oncological treatments and as a result their use has expanded widely. BRAF inhibitors (BRAFi) in recent years have played a central role in disease control of unresectable BRAF-mutated pediatric low-grade gliomas (LGG). Understanding the side effects of these drugs is crucial for clinical practice. The aim of the study was to investigate retrospectively the acute and long-term effects of vemurafenib on lipid metabolism in children treated for an LGG. Children (n=6) treated with vemurafenib at the mean age of 8.41±6.1 exhibited early alterations in plasma lipid profile as demonstrated after 1 month (n=4) by high plasma levels of Low-Density Lipoprotein (LDL 139.5±51.5,mg/dL), Total Cholesterol (TC 221.5±42.1,mg/dL) and Triglycerides (TG 107.8±44.4,mg/dL). Despite dietary recommendations, dyslipidemia persisted 3 months later (LDL 148.8±40.2,mg/dL; TC 238±36.5,mg/dL; TG 115±45.6,mg/dL; n=4) and at long distance follow-up (38±23,months) after treatment with vemurafenib: LDL 139.2±49.1,mg/dL; TC 216.5±38.4,mg/dL; TG 129.7±83.4 mg/dL. This potential side effect suddenly resolved itself in the only patient in which a change of therapy was made (to the combination of dabrafenib and trametinib). BMI was compatible with overweight/obesity at baseline (mean BMI-SDS 0.9±1.8) in 2 patient and normal in 4 patients: during follow-up BMI remained stable in 5 patients and increased in 1 patient. Our findings highlight that Vemurafenib could be associated with an increased risk of dyslipidemia independently of weight. This risk should be anticipated by the identification of high-risk patients and managed by close monitoring of metabolic parameters during routinely follow-up. The association of dabrafenib with trametinib seem not be associated to dyslipidemia, yet more data are needed to explore the hypothesis about the possible role to reduce the risk of dyslipidemia.

### LGG-36. ANALYSIS OF BRAF-RELATED MUTATIONS IN PEDIATRIC LOW-GRADE GLIOMA

Shaoqun Li, Mingyao Lai, Linbo Cai; Guangdong Sanjiu Brain Hospital, Guangzhou, Guangdong, China

BACKGROUND: Most pediatric low-grade gliomas (pLGGs) are driven by a single genetic event resulting in up-regulation of the RAS/MAPK pathway. BRAF-related mutations are the most freauent molecular alteration in the pathway. To explore BRAF-related mutations in pediatric low-grade glioma is helpful for clinical practice. METHODS: In this study, patients with low-grade glioma aged ≤18 years in Guangdong Sanjiu Brain Hospital were enrolled. All patients accepted the tests of BRAF-related mutations with tumor tissue by next-generation sequencing (NGS). Results: A total of 26 patients diagnosed low-grade glioma and underwent NGS detection were included in this study. The male to female ratio was 6:7, and the median age was 9.5 years. 8 patients had tumors located in the cerebral hemisphere, 6 in the third or fourth ventricle, 5 in the cerebellum, 4 in the optic pathway, and 3 in the brain stem. A total of 14 patients took BRAF-related mutations, such as BRAF-KIAA1549 fusion, BRAF p.V600E mutation and other fusion. BRAF-KIAA1549 fusion was detected in 7 patients with pilocytic astrocytoma or pilomyxoid astrocytoma. BRAF p.V600E mutation was detected in 6 patients, two of whom were pleomorphic xanthoastrocytoma. A rare genetic fusion, BCAS1-BRAF fusion, was detected in 1 patient who had brain stem ganglioglioma. Among the 26 patients, 2 patients without BRAF-related mutations had typical multiple cafe-au-lait macules and were diagnosed as NF1-pLGG. These patients were treated with surgery, radiation, chemotherapy and targeted therapy. Only 2 patients received targeted therapy by Trametinib, Vimofinib and Everolimus after progression of the tumor. However, due to the severity of the disease, they eventually died. CONCLUSIONS: More than half of pLGG patients have BRAF-related mutations, which have the opportunity for targeted therapy. However, the optimal timing of targeted therapy still needs further exploration.

### LGG-37. LONG-TERM OUTCOME, VISUAL MORBIDITY AND PROGNOSTIC FACTORS IN INFANTS AND YOUNG CHILDREN WITH OPTIC PATHWAY GLIOMA FROM THE GREAT ORMOND STREET HOSPITAL (GOSH) LGG - COHORT

Stefania Picariello[1], Brownen Walters[2], Richard Bowman[2], Olga Slater[3], Mette Jorgensen[3], Christine Dahl[3], Patricia O'Hare[4,3], Helen A. Spoudeas[5,6], Hong-Wei Gan[5], Kristian Aquilina[7], Yen Ch'in Chang[8], Felice D'Arco[9], Darren Hargrave[3], Enrico Opocher[10,3]; [1]Department of Paediatric Oncology, Napoli, Italy. [2]Ophthalmology Department, Great Ormond Street Hospital, London, United Kingdom. [3]Paediatric Oncology, Great Ormond Street Hospital, London, United Kingdom. [4]Paediatric Oncology, Belfast, United Kingdom. [5]Endocrinology Department, Great Ormond Street Hospital, London, United Kingdom. [6]section of molecular basis of rare disease, University College University, London, United Kingdom. [7]Paediatric Neurosurgery, Great Ormond Street Hospital, London, United Kingdom. [8]Radiotherapy Dep. UCLH, London, United Kingdom. [9]Department of Radiology, Great Ormond Street Hospital, London, United Kingdom. [10]Paediatric Hematology, Oncology and Stem Cell Transplant Division, Padua University Hospital, Padua, Italy

INTRODUCTION: The treatment aim of childhood optic pathway glioma (OPG) is visual preservation. However, long-term outcomes and prognostic factors implicated remain largely unknown. METHODS: We undertook a retrospective study of infants and young children (IYC) ≤3 years with OPG and logMAR visual acuity (VA) at baseline/follow-up. We derived Overall- (OS), Progression-free (PFS), Radiotherapy-free (RTFS) and Visual event-free survival (vEFS) curves and analysed prognostic factors for visual deterioration and WHO defined blindness (>1.3 logMAR both eyes). RESULTS: Of 81 IYC-OPG (147 evaluable eyes) baseline vision was below 5%ile for age in 33 (41%) and 27 (33%) in one or both eyes respectively, within normal range in 21 (26%). After observation (11), chemotherapy (66) or RT (4), radiological progression occurred in 47 (58%), multiple times in 34.6% (range 2 - 8) and 10yr-PFS was 39.8%. Twenty had RT after 4.2 years from diagnosis (10yr-RTFS 72.4%) and 12% died (10yr-OS 89%). After 8.9 years VA was better/stable/ worse in 36%/32%/32% of subjects, with median time to visual event of 1.7 years (range 0.16 - 12) and 10yr-vEFS 41.3%. Final VA was reduced (>0.2 logMAR) in 23 (28.4%) and 43 (53.1%) in only one or both eyes respectively. Amongst those with unilateral impairment 13/23 affected eyes had no useful vision (light/no light perception). Amongst those with bilateral impairment best eye VA was > 1.0 log MAR in 22/43 (LP/NLP in 10). Infants < 1 year had significantly inferior 10-yrPFS (5.6%), post-chiasmatic involvement was associated with visual deterioration (HR 2.91, 95%CI=1.1- 7.7), and baseline bilateral abnormal for age vision predicted WHO blindness at follow-up (OR 17.9, 95%CI=3.2 – 101.1). CONCLUSIONS: Many IYC-OPG suffer multiple progressions with significant long-term visual morbidity. Predictive factors such as age, tumor location and baseline age-adjusted vision allow patients' selection for early sight rehabilitation and consideration for experimental strategies preventing visual loss.

### LGG-38. DOSE-DEPENDENT SEIZURE CONTROL FOR AN NF1 PATIENT TREATED VIA MEK-INHIBITION FOR OPTIC PATHWAY GLIOMA

Evan Cantor, Ashley Meyer, Andrea Ogle, Margaret Shatara, Andrew cluster, Mohamed S. Abdelbaki, Stephanie Morris, Judith Weisenberg, Nicole M. Brossier; Saint Louis Children's Hospital, St. Louis, MO, USA

BACKGROUND: Low-grade gliomas (LGG) are the most common solid tumor of childhood and can result in neurologic complications, including seizures, focal neurologic deficits, and learning difficulties. Molecularly tar-

geted agents are increasingly being utilized to treat LGG, but the effect of these agents on accompanying neurologic complications are poorly understood. CASE: An 8-years old male with Neurofibromatosis Type 1 (NF1), medically refractory epilepsy and deep extensive glioma (extending from the optic pathway and involving the basal ganglia and corpus collosum) began selumetinib therapy due to radiographic and symptomatic tumor progression. Radiographic response (resolution of enhancement) was observed at 12 weeks of therapy, accompanied by improvement in seizure frequency, hemiparesis, and academic performance. Due to cardiotoxicity observed at that time (asymptomatic decreased ejection fraction and shortening fraction on echocardiogram), selumetinib was reduced to 50% dosing. On this reduced dose of selumetinib, seizures increased in frequency with subsequent worsening hemiparesis and recurrence of learning difficulties. One month later, dosing was escalated back to 100% due to interval resolution of cardiotoxicity, resulting in resolution of seizures and improvement in focal neurologic deficits and cognition. DISCUSSION: Dose-dependent response to MEK inhibition was observed without concurrent changes in anti-epileptic medications. The tumor was stable in size despite improved enhancement with treatment, suggesting that objective response by RANO criteria is not necessary for improved seizure control in LGG. Recent work has implicated the RAS/MEK/ERK pathway in neuronal precursor cells as a cause for epilepsy, suggesting that MEK inhibition of NF1-heterozygous neurons could be contributing to treatment response in this patient. Improvements in weakness and academic performance may have been due to improved seizure control or a direct effect of MEK inhibition on NF1-heterozygous neurons. CONCLUSION: MEK inhibition may have a clinically relevant anti-seizure effect for patients with pediatric LGG or NF1.

### LGG-39. ASCITES IN A MEDULLARY AND LEPTOMENINGEAL GANGLIOGLIOMA PATIENT FOLLOWING CISPLATIN TREATMENT NECESSITATING CESSATION OF THERAPY AND CONVERSION TO VA SHUNT

Evan Cantor, Andrea Ogle, Ashley Meyer, Margaret Shatara, Nicole M. Brossier, Mohamed S. Abdelbaki, Jennifer Strahle, Andrew Cluster; Saint Louis Children's Hospital, St. Louis, MO, USA

INTRODUCTION: Ganglioglioma is a low grade neoplasm consisting of dysplastic neuronal and neoplastic glial cells and accounts for 5% of pediatric CNS tumors. Management often includes CNS diversion. There have been case reports in which platinum containing chemotherapy has been thought to contribute to CSF malabsorption leading to ascites. CASE: A 13 month old male developed progressive macrocephaly, developmental delay, chronic emesis, and intermittent bilateral cranial nerve VI palsy over the 5 months prior to presentation. MRI brain/spine was significant for an enhancing nodule in the left posterior lateral medulla, nodular thickening and enhancement along the brainstem down to the conus medullaris and in the tentorium, with associated hydrocephalus. Biopsy of the medullary nodule and of the enhancement were consistent with ganglioglioma with BRAF-KIAA1549 fusion, equivocal MYCN amplification, and no BRAF V600E mutation. A ventriculo-peritoneal shunt was placed at the time of biopsy. Therapy was initiated with vincristine (1.5 mg/m2) and carboplatin (175 mg/m2.) Following the 12 week induction phase of therapy, he developed increasing diarrhea, emesis, and abdominal ascites. Peritoneal fluid analysis had no malignant cells and low protein compared to CSF. Ascites was responsive to drainage but would rapidly re-accumulate. Ultimately the patient's chemotherapy was discontinued after 2 maintenance cycles due to continued symptoms. Acetazolamide was trialed but discontinued due to side effects, so its efficacy could not be determined. He underwent shunt externalization followed by venticulo-atrial (VA) shunt re-internalization. He has not had ascites since that time, at 4 months from surgery. His CNS disease burden has been stable at 6 months off therapy. DISCUSSION: Ascites was most likely due to CSF malabsorption in the abdomen with a possible contribution from platinum containing chemotherapy and less likely secondary to malignant peritoneal cells. Resolution since VA shunt internalization makes alternate explanations less likely.

### LGG-40. GROWTH HORMONE REPLACEMENT IN CHILDREN ON THERAPY WITH VEMURAFENIB FOR LOW GRADE GLIOMA

Antonio Verrico[1], Marco Crocco[1], Emilio Casalini[2], Antonia Ramaglia[3], Andrea Rossi[3], Valentina Iurilli[4], Gianluca Piccolo[1], Claudia Milanaccio[1], Maria Luisa Garrè[1], Natascia Di Iorgi[2]; [1]Neuro-Oncology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy. [2]Endocrinology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy. [3]Neuroradiology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy. [4]Pharmacy, IRCCS Istituto Giannina Gaslini, Genoa, Italy

BRAF inhibitors (iBRAF) are a therapeutical option for pediatric Low-Grade-Gliomas (pLGG), but their chronic use may be needed to prevent tumor regrowth. Growth hormone (GH) replacement in children with GH deficiency (GHD) and on oncological treatment is under debate. We report on our experience of recombinant human GH (rhGH) replacement in two children (1 Female, 1 Male) which started Vemurafenib therapy, at 5 (F) and 9,25 (M) years of age, for recurrent/progressive chiasmatic-hypothalamic pLGG, with partial response (RANO criteria) and subsequent stable disease. A diagnosis of GHD was established at 9,2 (F) and 11,2 (M) years of age (GH peaks to stimulation tests <3mcg/L), 4,2 (F) and 1,9 (M) years after Vemurafenib start. Both patients were treated with GnRH analogues for precocious puberty. rhGH dose was titrated to 0.020 mg/kg/day during follow-up based on IGF-1 levels < +2 SDS. Height remained stable in both (F: -3,4SDS; M: 0SDS), with a mean growth velocity after 2 years around 6 cm/yr. BMI increased in the F (1,59 to 1,78 SDS) and decreased in the M (2,66 to 2,56 SDS); Dual-X-ray absorbiometry confirmed high fat mass at T0 (F:54,6%; M:48%) and at T24 (F:49,2%; M:48,1%). Lipid profile improved in both patients (F: Triglycerides 175 to 152 mg/dl, LDL 195 to 155 mg/dl; M: Triglycerides 138 to 118 mg/dl, LDL 147 to 147 mg/dl, at T0 and T24, respectively), while baseline blood glucose increased (F: 83 to 96 mg/dl; M 82 to 91 mg/dl). Residual tumor was stable in both patients. CONCLUSIONS: In 2 GHD patients due to pLGG and treated with Vemurafenib, two-years of low-dose rhGH showed beneficial effects on height stabilization and on lipid profile, and a different impact on body composition parameters; rhGH was safe and not associated with residual tumor growth.

### LGG-41. THE CLINICAL AND MOLECULAR LANDSCAPE OF GLIOMAS IN ADOLESCENTS AND YOUNG ADULTS

Julie Bennett[1], Liana Nobre[1], Javal Sheth[1], Scott Ryall[1], Karen Fang[1], Monique Johnson[1], Logine Negm[1], Jiil Chung[1], Martin Komosa[1], Nuno M. Nunes[1], Mary Jane Lim Fat[2], James Perry[2], Arjun Sahgal[2], Jay Detsky[2], Eric Bouffet[1], Lili Naz-Hazrati[1], Peter Dirks[1], Birgit Ertl-Wagner[1], Paul Kongkham[3], Gelareh Zadeh[3], Warren Mason[3], Seth Climans[4], Michael Cusimano[5], Sunit Das[5], Andrew Gao[3], Derek Tsang[3], Lananh Nguyen[5], Normand Laperriere[3], Julia Keith[2], David Munoz[5], Uri Tabori[1], Cynthia Hawkins[1]; [1]The Hospital for Sick Children, Toronto, Ontario, Canada. [2]Sunnybrook Health Sciences Center, Toronto, Ontario, Canada. [3]University Health Network, Toronto, Ontario, Canada. [4]London Health Sciences Center, London, Ontario, Canada. [5]Unity Health, Toronto, Ontario, Canada

OBJECTIVE: Gliomas in adolescents and young adults (AYA) are commonly treated with a standard chemo-radiation approach based on data from adults. The clinical impact of paediatric-type alterations in these tumours is unknown. METHODS: We compiled a multi-institutional cohort of patients diagnosed with glioma between 15-39.9 years over 20 years. Complete molecular analysis, therapeutic data and outcome was collected. For specific alterations, analysis included patients aged 0-39.9 years. RESULTS: A total of 1900 patients with 876 AYA gliomas were included. Ongoing analysis reveals genetic alterations in 95% of available tumours. IDH-mutant tumours account for only 53%, while paediatric-type mutations were found in 35% of AYA tumours with IDH-WT GBM accounting for the remaining 12%. The most common paediatric alterations in AYAs included BRAF p.V600E (11%) and FGFR alterations (6%) while BRAF fusions, H3 p.K27M and H3.3 p.G34R were rarely observed (4%, 4% and 1% respectively). BRAF fused tumours with non-canonical binding partners were enriched in AYAs. Analysis of BRAF-V600E gliomas between ages 0-40 revealed increased tendency for malignant tumours in patients >20 years suggesting malignant transformation possibly due to higher rate of secondary hits including TP53, CDKN2A and ATRX mutations. This resulted in worse overall-survival for AYA patients with BRAF-V600E glioma when compared to children under 20 years (p=0.0032). Ten-year OS of 100%, 90% and 95% was seen for BRAF fused, BRAF-V600E and FGFR-altered AYA low grade glioma respectively, compared to 14% and 25% for BRAF-V600E and FGFR-altered high grade glioma. In contrast, continuous decline was observed in the IDH-mutant gliomas with 10-year OS of 50% which declined to 29% at 15 years. CONCLUSIONS: Gliomas in AYA are enriched for paediatric-type alterations with distinct molecularly-based outcomes. As these tumours carry different outcomes than childhood glioma and may respond to targeted inhibitors, AYA gliomas would benefit from comprehensive diagnostic and therapeutic approaches.

### LGG-42. THROMBOEMBOLIC TOXICITY OBSERVED WITH CONCURRENT TRAMETINIB AND LENALIDOMIDE THERAPY

Priya Chan[1], Ashley Sabus[2], Molly Hemenway[3], Kathryn Chatfield[3], Nicholas Foreman[3], Nathan Dahl[3]; [1]Department of Pediatrics, University of Utah, Salt Lake City, UT, USA. [2]Department of Pharmacy, Children's Hospital Colorado, Aurora, CO, USA. [3]Department of Pediatrics, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

INTRODUCTION: Event-free survival of pediatric low-grade glioma (pLGG) is poor, and patients often require multiple treatment strategies. The hallmark of pLGGs are genetic aberrations of the mitogen-activated protein kinase pathway, which lead to constitutive pathway activation. MEK and