section followed by radiation and 5 cycles of pembrolizumab stable at 5th cycle. CONCLUSION: Children with NF1 stigmata and GBM can have concurrent NF1 and LS, or CMMRD with NF1 somatic mutations. Our patients tolerated alkylating agents, despite risk for secondary malignancies as upfront therapy and at recurrence checkpoint inhibitors. Upfront therapy in GBM with mismatch repair syndrome with checkpoint inhibitors should be studied.

NFB-07. USE OF PEGYLATED INTERFERON A- 2B IN PEDIATRIC PATIENTS AFFECTED BY UNRESECTABLE PLEXIFORM NEUROFIBROMAS: MONOCENTRIC EXPERIENCE

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BACKGROUND: Neurofibromatosis type 1 (NF1) is autosomal dominant neurogenetic disorder characterized by progressive cutaneous, neurologic, skeletal, and neoplastic manifestations. Plexiform neurofibromas (PN) are one of the different types of neurofibromas that occur in these patients. Complete surgical resection is difficult due to the tumor infiltrative behavior. We evaluated pegylated interferon- α-2b (PI) in patients with unresectable progressive or symptomatic PN. METHODS: Pediatric patients (1–21 years old) affected by unresectable PN, followed at Bambino Gesù Hospital, were treated with PI. We administered PI as a weekly subcutaneous injection at a beginning dose of 1.0 mcg/kg/wk, increased to 3.0 mcg/kg/wk if well tolerated. Paracetamol (15mg/kg) was given 30 minutes prior the dose of PI and then every 4–6 hours as needed. Patients were evaluated with Magnetic Resonance Imaging (MRI) every 12 months after treatment start in case of stable disease. RESULTS: 10 patients (3 females, 7 males) were enrolled. Median age was 12 years old. The median duration of treatment was 12,6 months. Grade 3 neutropenia (30%) and increased liver transaminases level (20%) were the most common toxicity. 6/10 patients experienced an improvement about pain. 7/10 patients showed clinical response. 1/10 patient had a radiological response at MRI, 1/10 experienced progression disease and 8/10 showed a stable disease at MRI evaluation. CONCLUSIONS: Our study demonstrated that PI could be a suitable treatment for unresectable PN in terms of stabilization of the tumour size due to its antitumor activity although clinical response does not correlate with radiographic changes.

NFB-08. PHASE II STUDY OF AXITINIB IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 2 AND PROGRESSIVE VESTIBULAR SCHWANNOMAS

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INTRODUCTION: Vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), and c-KIT represent clinically and/or preclinically validated molecular targets in vestibular schwannomas. We conducted a single institution, prospective, open-label, two-stage phase II study (ClinicalTrials.gov identifier NCT02129647) to estimate the response rate to axitinib, an oral multi-receptor tyrosine kinase inhibitor targeting VEGFR, PDGFR and c-KIT, in neurofibromatosis type 2 (NF2) patients with progressive vestibular schwannomas (VS). METHODS: NF2 patients older than 5 years with at least one volumetrically measurable, progressive VS were eligible. The primary endpoint was to estimate the objective volumetric response rates to axitinib. Axitinib was given continuously in 28-day cycles for up to of 12 cycles. Response was assessed every 3 months with MRI using 3-D volumetric tumor analysis and audiograms. Volumetric response and progression were defined as ≥20% decrease or increase in VS volume, respectively. RESULTS: Twelve eligible patients (ages: 14–56 years) were enrolled on this study. Seven of twelve patients completed 12 cycles (range: 2 to 12 cycles). We observed two imaging and three hearing responses. Best volumetric response was -53.9% after nine months on axitinib. All patients experienced drug-related toxicities, the most common adverse events were diarrhea, hematuria and skin toxicity, not exceeding grade 2 and hypertension, not exceeding grade 3. CONCLUSIONS: While axitinib has modest anti-tumor activity in NF2 patients, it is more toxic and appears to be less effective compared to bevacizumab. Based on these findings, further clinical development of axitinib for this indication does not appear warranted.

NFB-09. ENROLLMENT AND CLINICAL CHARACTERISTICS OF NEWLY DIAGNOSED, NEUROFIBROMATOSIS TYPE 1 ASSOCIATED OPTIC PATHWAY GLIOMA (NF1-OPG): PRELIMINARY RESULTS FROM AN INTERNATIONAL MULTI-CENTER NATURAL HISTORY STUDY

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INTRODUCTION: Because treatment and clinical management decisions for children with NF1-OPG remain challenging, we sought to establish evidence-based guidelines. We prospectively enrolled children with newly-diagnosed NF1-OPGs, and gathered standardized clinical neuro-oncology and ophthalmology assessments. METHODS: Only children with NF1 and newly diagnosed OPGs, confirmed by central review, were eligible. Indications for obtaining the initial MRI, as well as factors associated with the decision to treat with chemotherapy or observe without treatment, were obtained. Quantitative visual acuity (VA), other ophthalmic features, and imaging were captured at standard time points. Goal enrollment is 250 subjects. RESULTS: One-hundred thirty-three children (52% female) from 20 institutions met inclusion criteria, and were included in this preliminary analysis. Eighty-six percent of subjects were able to perform quantitative VA testing at enrollment. The most common reasons for the diagnostic MRI included screening related to NF1 diagnosis (36.8%), ophthalmologic concerns (29.3%), and non-ophthalmologic concerns (24.8%), such as headache. To date, twenty subjects have initiated treatment with chemotherapy, twelve (9%) at the time of the initial OPG diagnosis. Median age at OPG diagnosis was 3.1 years. Age and sex distribution were similar in subjects immediately entering the observation and treatment arms (median age 3.0 versus 3.5 years, respectively). CONCLUSION: Most children with NF1-OPGs are observed at time of their initial OPG diagnosis, rather than treated. Importantly, a large proportion of children are able to complete quantitative VA testing at enrollment. Once enrollment is complete, these data will help to establish evidence-based guidelines for clinical management of NF1-OPGs.

NFB-11. WHITE MATTER DIFFERENCES IN CHILDREN WITH NF1 COMPARED TO CONTROLS

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INTRODUCTION: Neurofibromatosis type 1 (NF1) is a genetic condition in which children develop learning challenges and glioma. White matter tracts (WMT) are implicated in these cognitive functions, while oligodendroglial precursor cells are implicated in both gliomagenesis and white-matter development. Specific WMTs have not been well characterized in NF1. METHODS: Twenty NF1 patients aged 1.4–17.6 years (M = 9.5 years, 24 male) and 20 age-and-sex-matched controls underwent dMRI at 3T (25 directions, b=1000 s/mm^2). Automated segmentation of WMTs extracted fractional anisotropy (FA) and mean diffusivity (MD) of 18 major WMTs. Covariance analysis examined the effect of group (NF1/controls) on FA/MD after controlling for intracranial volume. Regression analyses for WMTs determined the interaction of FA/MD with age for NF1 patients compared to controls. Significance was set at $p<0.05$ after correcting for multiple comparisons using false discovery rate. RESULTS: Compared to controls, children with NF1 had significantly decreased FA in 8 and increased MD in 12/18 tracts. Differences held after controlling for intracranial volume. The interaction between group and age accounted for a significant proportion of the variance in FA in 9 and in MD in 16/18 tracts. FA and MD differ-

ences between children with NF1 and controls were greater at younger than older ages. CONCLUSION: Microstructural differences were observed in WMTs in children with NF1 compared to controls. These differences were not explained by intracranial volume and were most pronounced in younger children with NF1 compared to controls. These findings have implications for understanding neurocognitive deficits and gliomagenesis observed in children with NF1.

NFB-12. TRAMETINIB THERAPY FOR PEDIATRIC PATIENTS WITH REFRACTORY LOW GRADE GLIOMA OR EXTENSIVE SYMPTOMATIC PLEXIFORM NEUROFIBROMA

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OBJECTIVE: Refractory symptomatic plexiform neurofibromas (PNF) and inoperable refractory low grade gliomas (LGG) pose a clinical challenge that may be life threatening. Phase 1 and 2 clinical trials of MEK inhibition with selumetinib in inoperable PNF and LGG have demonstrated promising results in pediatrics, however access has been limited to enrollment on clinical trial. Phase 1 clinical trial for trametinib a MEK 1 and 2 inhibitor has been completed, publication is pending. Thus we have treated a series of children on a compassionate basis with extensive PN or LGG refractory disease with trametinib, as this is available in Canada. METHODS: We have treated children with trametinib on a compassionate basis in our province since 2017. Review of the clinical data regarding this therapy has been IRB approved. RESULTS: Two young patients were treated for indication of life threatening extensive PNF and have had tumor shrinkage and improvement of clinical status. Treatment has been complicated by paronychiae, eczema exacerbation, chondrodermatitis nodularis helicis, RSV and influenza B infection and CTCAE grade 2 pneumonia. In spite of the side effects these two patients remain on treatment due to clear benefit from therapy including: improved respiratory compromise, hearing and dysphagia. We will present the data of additional patients treated with trametinib. CONCLUSION: Trametinib is an effective therapy for life threatening PNF by changing the natural history of tumor growth in young children. Further data is required in terms of tolerance, efficacy and durability of response in such patients in the setting of clinical trials.

NFB-13. TRAMETINIB FOR PLEXIFORM NEUROFIBROMA AND RECURRENT LOW-GRADE GLIOMA

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BACKGROUND: Based on early clinical efficacy data, Seattle Children's established a standard clinical practice for MEK inhibitor therapy for children with plexiform neurofibroma (PN) or recurrent low-grade glioma (LGG). METHODS: Data were collected under an IRB-approved retrospective chart review. Trametinib was prescribed off-label at 0.025 mg/kg daily for up to two years. Physical exam and laboratory monitoring were monthly for 3 months, then every 3 months. Retinal examination, ECHO/ECG were every 3 months. Tumor response was evaluated by MRI every 3 months for LGG; imaging for PN was dependent on tumor location. RESULTS: 30 patients received trametinib; 17 LGG, 16 PN (3 both); 22 with Neurofibromatosis, Type-1 (NF1); 16 female/15 male; median age 11 (range 4.1–22.6). Most common tumor location was optic pathway (n=11) and face/neck (n=10). Most common adverse events (AE) were dermatologic and gastrointestinal. Ten had dose interruption/reduction, only one discontinued therapy for AE. Six received dermatology specialty care for AE. With median follow-up of 12 months, only 3 patients had progression, one with NF1. One-year EFS was 100% for PN and 88%+7 for LGG. Driver mutations were identified in 9 of 10 tumors tested (5 BRAF fusion, 1 BRAFV600E, 1 FGFR1+NF1, 1 FGFR1+PTPN11, 1 NF1). Radiology review of response will be presented. CONCLUSIONS: This real-world pediatric cohort supports efficacy and tolerability of MEK inhibitor therapy for short-term control of plexiform neurofibroma and low-grade glioma with and without NF1. Further studies are warranted to evaluate comparative efficacy, combination therapy and duration of therapy.

NFB-14. PSYCHOSOCIAL OUTCOMES IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1 AND PLEXIFORM NEUROFIBROMAS

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OBJECTIVE: This case series seeks to examine neurocognitive outcomes, social-emotional functioning, and family burden in young children diagnosed with Neurofibromatosis, type 1 (NF1) with early growing plexiform neurofibromas (PNFs). BACKGROUND: Neurofibromatosis, type 1 (NF1) is a common predisposing chronic disease arising in early childhood, with an incidence of approximately 1:3000. Though NF1 displays a wide range of phenotypic variability, the primary feature of the disease is peripheral nerve sheath tumors called neurofibromas. Less is well known regarding the broader neurocognitive and social-emotional profile in presentations with more complex tumor growths, namely PNFs, which are present in at least half of the NF1-affected population. METHODS: Participants with NF1 and PNFs (n=2) aged 6-7years completed comprehensive neuropsychological evaluations and parents completed measures of quality of life, social-emotional/behavioral functioning of child, parental stress, family adaptability, and family cohesion. RESULTS: Outcomes suggest broad neurocognitive dysfunction (e.g., executive functioning deficits, attention problems, visual-motor delays, and poor motor coordination), social-emotional challenges (e.g., symptoms of anxiety and depression, and poor social skills), and familial distress. CONCLUSIONS: Findings indicate the value of early and frequent monitoring of children with PNFs in medical systems and multi-disciplinary teams, and the importance of early intervention for both children and families.

NFB-16. MTOROPATHIES AND SUBEPENDYMAL GIANT CELL ASTROCYTOMAS: PREDICTIVE VALUE OF GERMINAL TSC1/2 MUTATIONS SCREENING IN FAMILIAL CASES

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mTOR controls several important aspects of cell function particularly in the nervous system. Its hyperactivation has been involved in tuberous sclerosis complex (TSC) and other mTORopathies as well as drug-resistant epilepsy. Mutations in TSC1 and TSC2 genes cause loss of normal inhibition of mTORC1 complex, leading to cell overgrowth and disruptions in synaptogenesis. Many children and adults with TSC harbour neurologic defects especially subependymal giant cell astrocytomas (SEGAs) in the brain. Here, we have performed mutational analysis followed by a genetic counselling for a Tunisian family from Sfax town harboring epileptic seizures associated to a neurocutaneous disorder. Index cases were referred for renal angiolipomas (RAL) associated to seizures crisis and were diagnosed as having TSC. The first 26-year-old patient complained of epilepsy since the age of 22 with left temporal crisis related to cortical tubers near the Heschl's gyrus. His brother, a 36-year-old man presented more severe epileptic crisis (since 15 years-old), multiples RAL, subependymal nodules, and a rapid evolution of his mTORopathy with tumoral progression of his renal and central nerve lesions: renal cell carcinoma and SEGAs. TSC1 gene mutation screening showed heterozygous two bp deletion at codons 213 and 214 of exon 5. SEGAs are rare, low-grade glioneuronal brain tumors that occur almost exclusively in TSC patients but can lead to nervous complications. We showed through this report, the predictive value of germinal TSC mutations screening in familial cases, because early recognition of the molecular defect may lead to appropriate management of the tumoral progression.

NFB-17. MEK INHIBITOR BINIMETINIB SHOWS CLINICAL ACTIVITY IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1-ASSOCIATED PLEXIFORM NEUROFIBROMAS: A REPORT FROM PNOC AND THE NF CLINICAL TRIALS CONSORTIUM

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