knockdown alone did not affect sensitivity to carboplatin. Our findings further support a role for ATRX loss with subsequent ALT activation in a biologic subset of NF1-associated malignancies, thereby opening an opportunity for therapeutic targeting of these aggressive tumors using specific classes of drugs.

NFB-02. TREATMENT OF PAIN AND TUMOR GROWTH IN NF2

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BACKGROUND: Neurofibromatosis Type 2 (NF2) is an autosomal dominant disorder characterized by multiple nervous system tumors. Chronic pain affects the majority of patients with NF2 and is the primary factor that contributes to decreased quality of life. There are limited therapies that effectively reduce pain in NF2, but intravenous (IV) bevacizumab has been reported to provide significant relief to patients suffering from debilitating pain. CASE STUDY: James is a 24-year-old who initially presented with manifestations of NF2 at age 10, and by 15 years old had developed daily pain affecting his neck, back, and lower extremity. He has multiple CNS schwannomas, meningiomas, neurofibromas, and meets clinical NF2 criteria. While genetic testing did not reveal a mutation in his gDNA, low level skipping of exon 4 via RNA supports (likely mosaic) NF2. James's pain was poorly controlled with multiple oral medications, including opioids. James started IV bevacizumab at age 16 that improved his pain. He was critically dependent on bevacizumab for pain control and required continuous IV pain medication when bevacizumab was held for a surgical procedure. Following five years of bevacizumab he developed worsening toxicities including hypertension, proteinuria, and elevated hemoglobin. James transitioned to therapy with trametinib, a MEK inhibitor, and was able to wean off bevacizumab six months later. Treatment of NF2 related pain with trametinib instead of bevacizumab has improved his QOL with decreased medical visits, improved pain management, and decreased side effects. FUTURE IMPLICATIONS: Treatment of NF2 tumor related pain can be managed with MEK inhibitors.

NFB-03. TRAMETINIB FOR ORBITAL PLEXIFORM NEUROFIBROMAS IN YOUNG CHILDREN WITH NF1

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Plexiform neurofibromas (PN) in NF1 are diagnosed in early childhood and may grow rapidly during this period. In 10% of patients they involve the orbital-periorbital area and may cause visual problems including glaucoma and visual loss from amblyopia (deprivational, strabismic, or refractive), optic nerve compression or keratopathy. Ptosis, proptosis and facial disfigurement lead to social problems and decreased self-esteem. Complete surgical removal is usually impossible and there is a tendency for regrowth after debulking. Recently inhibitors of the RAS/MAPK pathway have been investigated for their activity in PN. We describe 5 young children with NF1 and PN of the orbital area treated with the MEK inhibitor trametinib followed clinically and by volumetric MRI. Treatment was initiated at mean age 26.8 months (SD ±12.8) and continued for median 25 months (range 17– 48). Reasons for initiating treatment were visual compromise and progressive tumor growth. Doses were as recommended. One child reported decreased orbital pain after one week and another, with involvement of the masseters, had increased ability to chew food. Toxicities were mostly to skin and nails grades 1–2 as expected. Additionally, 60% had debulking surgery of preseptal eyelid tumor in first year of medical treatment. Volumetric MRI measurements showed reduction of 8–26% at 1 year from baseline with a maximal reduction of 45% in two patients at 22 & 45 months. No change in visual function was recorded following treatment initiation. In conclusion, trametinib may decrease tumor size in young children with orbital PN and may prevent progressive disfigurement.

NFB-04. EXAMINING DIFFUSION, ARTERIAL SPIN-LABELED PERFUSION, AND VOLUMETRIC CHANGES IN THE NEUROFIBROMATOSIS TYPE 1 BRAIN USING AN ATLAS-BASED, MULTI-PARAMETRIC APPROACH

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BACKGROUND: Neurofibromatosis Type 1 (NF1) is a multisystem disorder with wide ranging clinical implications. Patients may present with macrocephaly, stroke, and cognitive deficits, all of which may impede normal neural development. We applied atlas-based, multi-parametric MRI analysis of regional brain to evaluate diffusion, arterial spin-labeled (ASL) perfusion, and volumetric changes in children with NF1. METHODS: Children evaluated for NF1 from 2009 to 2018 at Stanford University (n=78) were retrospectively reviewed and compared to healthy controls (n=100). All patients underwent diffusion-weighted (DWI) magnetic resonance imaging at 3T, and children with brain tumors were excluded. Using atlas-based DWI analyses, we assessed volume, median apparent diffusion coefficient (ADC), and cerebral blood flow in the cerebral cortex, thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, nucleus accumbens, brain stem, and cerebral white matter. We also measured volume of the lateral ventricles. Multivariate analysis of covariance was used to test for differences between controls and NF1 patients, controlling for gender and age at time of imaging. RESULTS: Comparing NF1 to controls, we detected increased volume and decreased ASL cerebral blood flow in white matter and all subcortical and cortical structures except for brainstem volume. Median ADC was also increased in the thalamus, pallidum, hippocampus, and brainstem. CONCLUSIONS: Using a multi-parametric approach, we demonstrate quantitative measures of microstructural and physiologic changes of the NF1 brain. Atlas-based, quantitative MRI brain signatures may serve as biomarkers of neural development and further provide insight into associated cognitive dysfunction or risks for vasculopathy-related strokes in children with NF1.

NFB-05. AN UNUSUAL PRESENTATION OF RECURRENT LANGERHANS CELL HISTIOCYTOSIS OF THE CRANIOFACIAL BONES IN A PATIENT WITH NEUROFIBROMATOSIS TYPE I

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Neurofibromatosis type 1 (NF1), predisposes patients to benign and malignant tumors due to lack of suppression of the mitogen activated protein kinase (*MAPK*) signaling pathway. Langerhans cell histiocytosis (LCH) manifests in numerous ways, from localized lesions to multisystem organ involvement secondary to a constitutively active *MAPK* signaling cascade often driven by *BRAF* mutations. While both LCH and NF1 are characterized by overactive *MAPK* signaling, there are few reports of the two diseases occurring simultaneously. We report a novel case of a patient with underlying NF1 and recurrent LCH without a *BRAFV600E* mutation. She initially presented at 2 years of age with an aggressive appearing mass of the left temporal bone found on surveillance imaging. Pathology was consistent with Langerhans histiocytosis and she was treated with the LCH-III protocol for patients with high-risk LCH due to the location of her lesion. Five years after completion of therapy, MRI demonstrated development of a calvarial mass consistent with relapsed LCH in a new risk site. Lesional curettage was performed and pathology confirmed recurrence of LCH with juvenile xanthogranulomatous features. *BRAF* testing of blood and the lesion were negative for any *BRAF* alterations. Further genomic evaluation of the tumor is in progress at this time to evaluate for other known mutations associated with LCH. The patient is currently receiving monthly cytarabine treatment which she has tolerated to date. Our patient represents a unique presentation of recurrent LCH in a patient with NF1 and further molecular evaluation may help identify other drivers of LCH activation.

NFB-06. TREATMENT CHALLENGES IN PEDIATRIC GLIOBLASTOMA MULTIFORME WITH CONCURRENT SOMATIC AND GERMLINE NF1 MUTATIONS WITH GERMLINE MISMATCH REPAIR MUTATIONS: TWO UNIQUE CASES

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INTRODUCTION: We report the first known cases of pediatric glioblastoma (GBM) with prior clinical NF1 diagnoses, one with concurrent germline Lynch syndrome (LS) and NF1, and the other with somatic NF1 mutation and germline constitutional mismatch repair deficiency (CMMRD). METHODS: Two pediatric GBM cases with prior NF1 clinical diagnoses based on neurocutaneous criteria were reviewed. Next generation sequencing and immunohistochemical staining were used for somatic and germline *NF1* and MMR gene mutation detection, and for MMR protein expression, respectively. RESULTS: Sixteen year old male with prior NF1 clinical diagnosis had resection of right frontal GBM revealing somatic mutations of POLE and PMS2, but not NF1. His father had confirmed LS with MSH2 mutation and no neurocutaneous stigmata. Patient's germline testing revealed both pathogenic MSH2 plus NF1 mutations confirming LS and NF1. Treatment consisted of chemoradiation with temozolomide followed by adjuvant temozolomide with stable disease at 8 cycles. Nineteen year old male with former NF1 clinical diagnosis had 2 GBMs, first in left midbrain biopsied revealing somatic PMS2 and NF1 mutations underwent radiation then 7 cycles of temozolomide, then new left frontal GBM underwent re-

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-