using mRNA to titrate CAR T cell therapy in the brain, and establish GD2-directed mRNA CAR T cells as a safe and effective method for treating DMG.

LOW GRADE GLIOMAS

LGG-01. *NF1* MUTATION DRIVES NEURONAL ACTIVITY-DEPENDENT OPTIC GLIOMA INITIATION

Yuan Pan[1], Jared Hysinger[1], Nicki Schindler[1], Olivia Cobb[2], Xiaofan Guo[2], Belgin Yalçın[1], Corina Anastasaki[2], Sara Mulinyawe[1], Anitha Ponnuswami[1], Suzanne Scheaffer[2], Yu Ma[2], Kun-Che Chang[1], Xin Xia[1], Joseph Toonen[1], James Lennon[1], Erin Gibson[1], Linda Liau[3], Jeffrey Goldberg[1], Michelle Monje[1], and David Gutmann[2]; [1]Stanford University, Stanford, CA, USA, [2]Washington Unviersity, St. Louis, MO, USA, [3]UCLA, Los Angeles, CA, USA

Neurons have recently emerged as essential cellular constituents of the tumor microenvironment, where their activity increases the growth of a diverse number of solid tumors. While the role of neurons in tumor progression has been previously demonstrated, the importance of neuronal activity to tumor initiation is less clear, particularly in the setting of cancer predisposition syndromes. In the Neurofibromatosis type 1 (NF1) cancer predisposition syndrome, in which tumors arise in close association with nerves, 15% of individuals develop low-grade neoplasms of the optic pathway (optic gliomas) during early childhood, raising the intriguing possibility that postnatal light-induced optic nerve activity drives tumor initiation. Here, we employ an authenticated murine model of *Nf1* optic glioma to demonstrate that stimulation of optic nerve activity increases optic glioma growth, while decreasing optic nerve activity via light deprivation prevents tumor formation and maintenance. By manipulating environmental light to modulate optic pathway (retinal) neuron activity, we show that *Nf1* optic glioma initiation depends on neuronal activity during a developmental period susceptible to tumorigenesis. Germline *Nf1* mutation in retinal neurons results in aberrantly high optic nerve neuroligin-3 (Nlgn3) shedding in response to retinal neuronal activity. Moreover, genetic *Nlgn3* loss or pharmacologic inhibition of Nlgn3 shedding blocks murine *Nf1* optic gliomagenesis and progression. Collectively, these studies establish an obligate role for neuronal activity in the development of certain brain tumors, elucidate a therapeutic strategy to reduce optic glioma incidence or mitigate tumor progression, and underscore the role of *Nf1* mutation-mediated dysregulation of neuronal signaling pathways in the NF1 cancer predisposition syndrome.

LGG-02. PEDIATRIC LOW-GRADE GLIOMA RISK STRATIFICATION IN THE MOLECULAR ERA

Jessica Hata[1], Mustafa Barbour[2,3], and Michael Angelo Huang[2,3]; [1]Norton Children's Hospital, Louisville, KY, USA, [2]Norton Children's Cancer Institute, Louisville, KY, USA, [3]University of Louisville School of Medicine, Louisville, KY, USA

Background: Pediatric low-grade gliomas (LGG), in particular those not amenable to surgical resection, are a therapeutic challenge owing to their heterogeneity in clinical behavior. Identification of the RAS/MAPK pathway as a universal feature of these tumors has led to an improved understanding and the development of targeted therapeutics. We examined the impact of known biological and novel molecular risk factors on patient outcomes at our institution. Methods: We retrospectively reviewed risk factors and clinical outcomes in 38 LGG cases diagnosed by histopathology at Norton Children's Hospital in Louisville, KY, USA from March 2015 to Jan 2019. Progression free survival (PFS) rates were generated using the Kaplan-Meier method. Log-rank tests and hazard ratios were used to identify prognostic factors by univariable analysis. Results: Among previously described biological risk factors, subtotal resection/biopsy only (HR 3.67, p=0.0257), non-WHO Grade I histology (HR 3.34, p=0.0101), and infant age (< 3 years) (HR 4.19, p=0.0031) were associated with shorter PFS. Brainstem location had no significant impact on PFS. (HR 0.86, p=0.8071). H3K27M mutant status was predictably associated with worse PFS (HR 5.86, p=0.0012). BRAF v600e mutant status, however, was not associated with inferior outcomes. On the contrary, in our study population, BRAF v600e mutant status had a suggested protective effect (HR 0.14, p=0.0247). Patients with 2 or more oncogenic driver mutations demonstrated worsened PFS (HR 4.78, p=0.0059). We utilized the following scoring system for risk stratification: 1 point was allocated for each of the above biological and molecular risk factors except for H3K27M, which was allocated 3 points. A score of < 3 was designated low risk. Non-low risk classification was associated with significantly inferior PFS (median PFS 13 vs. 62 mos, HR 4.26, p=0.0012). Conclusion: We herein demonstrate the utility of a combined biological and molecular risk classification for pediatric LGG.

LGG-03. LONG-TERM FOLLOW UP OF TARGETED THERAPY IN PEDIATRIC LOW-GRADE GLIOMAS: THE DANA-FARBER/BOSTON CHILDREN'S EXPERIENCE

Jessica Tsai[1], Jayne Vogelzang[1,2], Cecilia Sousa[1,2], Kee Kiat Yeo[1], Keith Ligon[1,2], Pratiti Bandopadhayay[1], and Tabitha Cooney[1]; [1]Dana-Farber/Boston Children's Cancer and Blood Disorder Center, Boston, MA, USA, [2]Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA

Background: Pediatric low grade gliomas (pLGGs) are the most common central nervous system (CNS) tumor in children and characterized by alterations in the MAPK pathway. Standard of care is not well defined, and treatment has evolved over the last decade to include molecular targeted therapies. The impact of targeted agents on the natural history of pLGGs remains unknown. We present a retrospective review of patients receiving targeted agents integrated with molecular profiling. Methods: We performed an IRB-approved, retrospective chart review of pLGGs treated with off-label use of dabrafenib, vemurafenib, everolimus, and trametinib at Dana-Farber/Boston Children's Cancer and Blood Disorders Center from 2010 to 2020. Results: Forty-nine patients were identified (dabrafenib n=9, everolimus n=27, trametinib n=10, and vemurafenib n=3). All patients receiving BRAF inhibitors harbored BRAF V600E mutation. Targeted agent was used as first-line therapy for 25% of patients, while for 31% of patients, targeted agent was second-line therapy. The median time from diagnosis to targeted therapy initiation was 4.76 years (0.10 – 23.77), median duration of targeted therapy was 0.79 years (0.01 – 4.87), median time to subsequent therapy post first-line targeted therapy was 0.2 years (0.01 – 3.33), and overall median follow-up for the entire cohort was 3.09 years (0.36 – 11.87). The 1-year, 3-year, and 5-year EFS from targeted therapy initiation was 58.0%, 32.2%, and 26.9%, respectively. Survival analyses by molecular subgroup and agent were performed. Reasons for cessation of targeted therapy included toxicities, progression, and/or planned end of therapy. Conclusions: Further efforts are ongoing to perform volumetric analysis of growth rates before, during, and after treatment. While targeted molecular therapies show great promise, it will be critical to understand how these agents alter the natural history of pLGGs, particularly in the context of genomic profiling.

LGG-04. MULTIOMIC ANALYSIS OF MAPK PATHWAY ACTIVITY IN PEDIATRIC PILOCYTIC ASTROCYTOMA

Romain Sigaud[1,2], Florian Selt[1,2], Thomas Hielscher[3], Anja Stefanski[4], Nina Overbeck[4], Diren Usta[1,2], Daniela Kocher[1,2], Marc Remke[5,6], Daniel Picard[5,6], Stefan M. Pfister[1,7], David T.W. Jones[1,8], Tilman Brummer[9], Olaf Witt[1,2], and Till Milde[1,2]; [1]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany, [2]Clinical Cooperation Unit Pediatric Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany, [3]Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany, [4]Molecular Proteomics Laboratory (MPL), Biological-Medical Research Center (BMFZ), Heinrich-Heine University Düsseldorf, Düsseldorf, Germany, [5]Department of Pediatric Oncology, Hematology, and Clinical Immunology, Medical Faculty, University Hospital Düsseldorf, Düsseldorf, Germany, [6]Department of Neuropathology, Medical Faculty, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany, [7]Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), Heidelberg, Germany, [8]Pediatric Glioma Research Group, German Cancer Research Center (DKFZ), Heidelberg, Germany, [9]Institute of Molecular Medicine and Cell Research (IMMZ), Faculty of Medicine, University of Freiburg, Freiburg, Germany

Introduction: Pilocytic astrocytomas (PA) are the most common pediatric brain tumors. They are characterized by MAPK pathway alterations, leading to its constitutive activation and modulating the balance between cell proliferation and the oncogene-induced senescence (OIS) sustained by senescence-associated secretory phenotype (SASP) factors. This makes PA suitable for MAPK inhibitor (MAPKi) therapies, showing encouraging results in phase 1/2 clinical trials. Little is known about the molecular implications of MAPK downregulation in the proliferating and senescent compartments. Methods: DKFZ-BT66 PA cells derived from a primary KIAA:BRAF-fusion positive PA cell line, were used as model system. Gene expression and phospho-proteomic datasets were generated from DKFZ-BT66 cells, in both the proliferative and senescent states, and treated with the MEKi trametinib for different time-spans. A time course analysis based on differentially expressed genes was performed, followed by a single-sample gene set enrichment analysis (ssGSEA). Analysis of the phospho-proteomic data is ongoing. Results: Differential gene expression analysis revealed that MEK inhibition leads to the inhibition of the OIS-SASP gene program in senescent DKFZ-BT66. ssGSEA showed that most