Introduction: In the last decade, checkpoint inhibitor-based immunotherapy has been a groundbreaking development in the treatment of cancer. However, only a subset of patients treated with immune checkpoint inhibitors show long-lasting clinical benefit. Studies showed the tumor immune microenvironment (TME) as a particularly important factor influencing treatment response, critical for the design of other or combinatorial immunotherapy treatment strategies. Extensive research has been performed in the adult cancer field to unravel its immunogenetic aspects. Further, in pediatric cancer this insight into tumor-immunofluting immune components is still lacking. This study aims to provide insight into the landscape of the immune microenvironment in pediatric primary nervous system tumors. Methods: Bulk RNA-seq data of 936 pediatric primary solid tumors is used. RNA-seq data is derived from multiple international initiatives including Therapeutically Applicable Research To Generate Effective Treatments (TARGET), the International Cancer Genome Consortium (ICGC) and the Children's Brain Tumor Tissue Consortium (CBTTC) were included in this study. We applied computational tumor immune microenvironment deconvolution, repurposed RNA-seq data to recover infiltrating T- and B-cell clonotypes and studied checkpoint gene expression across pediatric neural tumors. Results: Among pediatric neural tumors, embryonal tumors with multilayered rosettes (ETMR) and medulloblastomas (MB) were least immune infiltrated. Neuroblastomas (NBL) had the highest T-cell infiltration among pediatric cancers, while tumor mutational burden (TMB) was associated with immune cell infiltration in adult lung cancers and melanomas, we found no significant associations in pediatric cancers. The majority of NBL samples expressed LAG3, but ~10% of samples had elevated levels of TIM3 gene expression, suggesting a distinct mode of immunosuppression in this subset.

Background: Programmed cell death protein 1 (PD-1) is a co-inhibitory receptor mainly expressed on T cells. PD-1 antagonist antibodies have shown clinical benefit in multiple cancer types. However, the use of PD-1 antagonists in TINs, particularly glioblastoma (GBM) remains controversial. Here we investigated the clinical response of patients with TINs treated with PD-1 antagonists and assessed the associated biological mechanisms.

Methods: We performed a retrospective analysis of patients with GBM treated with PD-1 antagonists in the Children's Brain Tumor Network (CBTN). We identified 7 patients treated with PD-1 antagonists (n=7) and compared their outcomes to a control cohort of 21 patients treated with standard of care therapies for GBM (n=21).

Results: All patients treated with PD-1 antagonists experienced disease progression during the treatment phase, with median progression-free survival of 4 months. Three patients (43%) achieved a partial response (PR) or stable disease (SD). One patient achieved a complete response (CR). The remaining patients (57%) experienced disease progression while on treatment. The median overall survival (OS) was 12 months in the PD-1 antagonist cohort and 18 months in the control cohort. The median OS of patients achieving a PR or SD was 18 months, compared to 6 months in patients with disease progression on PD-1 antagonists.

Conclusion: Despite the promising preclinical and early clinical data, the clinical benefit of PD-1 antagonists in GBM remains limited. Further investigation is needed to identify predictive biomarkers and optimal treatment strategies for this patient population.
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 NEURAL ACTIVITY-DEPENDENT OPTIC GLIOMA INITIATION

Xuan Pan1,2,3, M. Ben Hassen1,4, C. W. Lung5,6,7, Nicki Schiavone1,2, Olivia Cob2, Xiaofan Guo2, Belgin Yalcın1, Corina Anastassiaki2, Sara Mulinyawe1, Anitha Ponnuswami1, Suzanne Schaeffer7, Yu Ma2, Kun-Cheng Chang1, Xin Xia7, Joseph Toonen1, James Lennon5, Erin Gibson1, Linda Liau1, Jeffrey Goldberg1, Michelle Mong1, and David Gutmann1,2,4,7,8, David T.W. Gutmann3,2,1

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 review of pLGGS treated with off-label use of dabrafenib, vemurafenib, everolimus, and trametinib at Dana-Farber/Boston Children's Cancer and Blood Disorder Center from 2010 to 2020. Results: Forty-nine patients were identified (dabrafenib n=9, vemurafenib n=10, and vemurafenib+ and/or everolimus+ n=30, 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 (HR 0.45, 95% CI: 0.27 – 0.76, p=0.0056). We used a primary KIAA:BRAF-fusion positive PA cell line, were used as model system. Gene expression and phospho-proteomic data is ongoing. Results: Differential gene expression was evaluated by a single-sample gene set enrichment analysis (ssGSEA). Analysis of the molecular implications of MAPK downregulation in the proliferating and senescent states, 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 cells, in both the proliferative and senescent states, and a primary KIAA:BRAF-fusion positive PA cell line, were used as model system. Gene expression and phospho-proteomic datasets were generated from DFKZ-BT66 cells, in both the proliferative and senescent states, and treated with the MEKi trametinib for different time-spans. A time course analysis was performed on differential gene expression. Gene expression analysis was 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 DFKZ-BT66. ssGSEA showed that most 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 Tsai1, Jayne Vogelzanger2, Cecilia Sousa2-3, Kee Kiat Yeo4, Keith Johnson2-3, Pratini Bandopadhyay1, and Tabitha Cooney1-2, Dana-Farber/Boston Children’s Cancer and Blood Disorder Center, Boston, MA, USA, 2Department 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 review of patients receiving targeted agents with off-label use of dabrafenib, vemurafenib, everolimus, and trametinib at Dana-Farber/Boston Children’s Cancer and Blood Disorder Center from 2010 to 2020. Results: Forty-nine patients were identified (dabrafenib n=9, vemurafenib n=10, and vemurafenib+ and/or everolimus+ n=30, 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 (HR 0.45, 95% CI: 0.27 – 0.76, p=0.0056). We used a primary KIAA:BRAF-fusion positive PA cell line, were used as model system. Gene expression and phospho-proteomic datasets were generated from DFKZ-BT66 cells, in both the proliferative and senescent states, and treated with the MEKi trametinib for different time-spans. A time course analysis was performed on differential gene expression. Gene expression analysis was 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 DFKZ-BT66. ssGSEA showed that most