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BACKGROUND: Recent insights highlight how the initiation and growth of gliomas is governed by interactions between glioma stem-like cells and stromal and immune cells in the tumor microenvironment. For pilocytic astrocytomas, the most common pediatric CNS tumor, this relationship is so far less explored. To this end, we used transcriptomic methods to investigate inter-patient heterogeneity, and the stromal and immune microenvironment of pilocytic astrocytomas. MATERIALS AND METHODS: In this study, we collected clinical data and tissue of 90 pre-treatment pilocytic astrocytomas from different CNS compartments: posterior fossa (n=57), supratentorial (n=23), and spinal (n=10). The median age at primary resection was 8 (0-16) years, and 66% (n=59) of our cohort was male. From 10 of these patients, we collected post-treatment samples after re-growth of the tumor as well. We characterized all samples by bulk RNA-sequencing and DNA methylation profiling, and selected a subset (n=10) samples for single-nucleus RNA-sequencing. RESULTS: Principal component analysis and unsupervised clustering of bulk sequencing data revealed gene expression patterns correlating to the CNS location of the tumor, consistent with prior reports. Using differential expression and functional pathway analysis, we found CNS region-associated enrichment of cell-cycle, developmental, and inflammatory-related pathways. With respect to the glioma immune microenvironment, supratentorial tumors were enriched in genesets related to T-cell activation and cytotoxicity, while spinal tumors had lowest expression of immune-related genes. Moreover, spinal tumors were enriched in pathways related to cell division, nucleotide synthesis, and neurodevelopment. To resolve cell-type expression programs of glioma and immune cells in the microenvironment, we collected and analyzed snRNA-seq data of 10 pilocytic astrocytomas, as well as harmonized our findings with a pre-existing dataset from Vladoiu, 2019. CONCLUSION: Our integrative transcriptomic analysis of pilocytic astrocytomas highlights CNS region-associated differences in expression programs of the glioma cells and in the immune cell composition of the tumor microenvironment.

IMMU-06. LANDSCAPE OF ADAPTIVE IMMUNITY OF CHILDHOOD BRAIN CANCERS

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T lymphocytes have a unique ability to recognize a vast array of antigens prompted by an enormous T cell receptor (TCR) repertoire. Characterization of tumor-infiltrating T cells (TILs) is key to understand MHC-restricted anti-tumor immunity and for developing T cell-centered immunotherapies such as adoptive cell therapy and tumor vaccines. In the current work, we investigated RNA-Seq data from 997 pediatric brain tumor patients and performed a large-scale comprehensive examination of the immunogenomic and TCR landscape of TILs across the entire spectrum of pediatric brain tumors. We show that the relative ratio between T cell diversity (clonality) and T cell abundance within each sample, represented by the clonal expansion index (CEI), is a strong predictor of prognosis both within and between tumor types. Interestingly, we show that CEI was strongly associated with molecular subgroups of medulloblastoma but not with known tumor-genomic features of these subgroups. Investigation of TCR clones recognizing a common recurrent tumor-antigen across patients based on CDR3 homology and characteristics, reveals 9 TCR clusters which are tumor type restricted with defined prognoses and HLA dominance. Using computational immunogenomics and machine learning-based investigations of these clusters yielded novel putative HLA-restricted tumor antigens which could bind and activate the clusters' specific TCRs. Importantly, our framework grounded the foundations for developing a precision medicine approach of T cell-centered immunotherapies. These findings have major implications for understanding the interplay between T cell and tumor genomic, and for developing new immunotherapies for children with brain tumors.

IMMU-07. INTERIM ANALYSIS OF THE HIT-HGG REZ IMMUNVAC STUDY - DENDRITIC CELL VACCINATION WITH PARTIAL T_{REG} DEPLETION AND DOUBLE CHECKPOINT BLOCKADE IN CHILDREN WITH RELAPSED HIGH-GRADE GLIOMAS.

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Relapses of high-grade gliomas show an aggressive course and survival 6 months after (sub-)total re-resection was only 62% in former HIT-HGG trials. Immunotherapy by induction of tumor-specific T cells through active immunization might help to control glioma regrowth. In the HIT-HGG-Rez Immunovac trial (Eudra-CT 2013-000419-26) we investigate whether a therapeutic vaccine (autologous dendritic cells loaded with tumor lysate, DCV) combined with T_{reg}-depletion and double checkpoint-inhibition (CI, anti-PD-1/anti-CTLA4) is able to increase the number of patients alive 6 months after relapse. Here, we report interim results after 50% of the intended patients (n=25) have been recruited. 13 children and adolescents (mean age 12.7±4.0 y) with relapsed glioblastomas were screened for the trial so far. Three patients were screening failures, 10 patients received study treatment. Of these, 2 patients are currently vaccinated, so that 8 patients were evaluable for this interim analysis. 5 SAEs have been reported so far, none of them was limiting. 4 patients with gross total or subtotal resection at time of relapse had an overall survival (OS) of 13.2±4.0 months and a 6-month survival rate of 100%, which compares favourably to historical controls. 4 partially resected patients survived only 5.1±1.3 months and 6-months OS was 25%. T_{reg}-depletion lead to a reduction of CD4+CD127-CD25+ T-cells of 45%, the majority of patients exhibited a tumor-specific T-cell response. We conclude that DCV in combination with partial T_{reg}-depletion and CI is feasible, safe, and related with immunological responses. Double CI was not associated with unexpected toxicities. In (sub-)totally resected patients, immunotherapy seems to confer a survival advantage. For the completion of the trial we aim to include more patients with (sub-)totally resectable tumors to gain more insight into the nature and duration of the induced immune response. This trial is supported by Bristol Myers-Squibb (CA209-7JA).

IMMU-08. NIVOLUMAB WITH OR WITHOUT IPILIMUMAB IN PEDIATRIC PATIENTS WITH HIGH-GRADE CNS MALIGNANCIES: EFFICACY, SAFETY, BIOMARKER, AND PHARMACOKINETIC RESULTS FROM CHECKMATE 908

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BACKGROUND: Limited data exist regarding checkpoint inhibitor efficacy for pediatric CNS malignancies. METHODS: CheckMate 908 is an open-label, sequential-arm, phase 1b/2 study investigating nivolumab (NIVO) and NIVO + ipilimumab (IPI) in 5 cohorts of pediatric patients previously treated with standard-of-care (NCT03130959). Patients received NIVO-3mg/kg Q2W or NIVO-3mg/kg + IPI-1mg/kg Q3W (4 doses) followed by NIVO-3mg/kg Q2W. Primary endpoints included OS (newly diagnosed DIPG) and PFS (other CNS cohorts); secondary endpoints included other efficacy metrics/safety. Exploratory endpoints included pharmacokinetics/biomarker analyses. Comparisons between treatments/cohorts were not planned. RESULTS: At data cutoff (13-Jan-2021), 166 patients received NIVO (n=85) or NIVO+IPI (n=81) at median (m) ages of 10.0yrs (range, 1-21) and 11.0yrs (1-21), respectively. In newly diagnosed DIPG, mOS (80% CI) was 11.7mos (10.3-16.5) with NIVO (n=23) and 10.8mos (9.1-15.8) with NIVO+IPI (n=22). In recurrent/progressive HGG, mPFS (80% CI) was 1.7mos (1.4-2.7) with NIVO (n=16) and 1.3mos (1.2-1.5) with NIVO+IPI (n=15). In relapsed/resistant medulloblastoma, mPFS (80% CI) was 1.4mos (1.2-1.4) with NIVO (n=15) and 2.8mos (1.5-4.5) with NIVO+IPI (n=15). In relapsed/resistant ependymoma, mPFS (80% CI) was 1.4mos (1.4-2.6) with NIVO (n=12) and 4.6mos (1.4-5.4) with NIVO+IPI (n=10). In other recurrent/progressive CNS tumors, mPFS (95% CI) was 1.2mos (1.1-1.3) with NIVO (n=19) and 1.6mos (1.3-3.5) with NIVO+IPI (n=19). Median treatment duration was 2.1mos (range, 0-41.7+ [NIVO]/0-29.6+ [NIVO+IPI]). Grade 3/4 treatment-related AEs occurred in 14.1% (NIVO) and 27.2% (NIVO+IPI) of