MAP2, NeuN, Olig-2, Synaptophysin, S-100 and Vimentin was performed for (n=12) tumors. We finally collected clinical data to preliminarily characterize this novel tumor entity. RESULTS: A selected analysis of the tumors in this novel cohort (n=68), compared with a reference cohort consisting of 15 other low- and high-grade glial and glioneuronal tumor classes, confirmed a clearly distinct grouping. No similarity was seen with the MN1:BEND2 and MN1:CXXC5-fused CNS-tumors. Analysis of Copy number profiles derived from the DNA-methylation data showed a mostly quite genome, with (n=64/65, 98%) of tumors showing copy number variations on Chromosome 22. RNA-sequencing detected PATZ1 fusions in all tumors sequenced (n=12; MN1:PATZ1, n=11; EWSR1:PATZ1). IGF2, PAX2 and GATA2, all genes involved in brain stem cell biology, were upregulated compared to a combined reference cohort of other glioma subtypes. DNA-sequencing showed no relevant alterations at the level of point mutations or small insertions/deletions. The tumors in our cohort showed polyphenotypic histologies along the glial spectrum, with a subset of tumors being diagnosed as Gliobastoma, WHO Grade 4 and bi- and multiphasic differentaion patterns being evident. IHC performed on tissue available did not favor a particular lineage, with most tumors showing immunopositivity to GFAP. Reverse translation of the gene expression data showed a potential role for NG2 as immunostaining marker. The median age was 11.0 years (0–80), (MN1:PATZ1 manifested at a younger age (median = 4 years) vs EWSR1:PATZ1 (median = 14 years)). Median PFS was 12 months. CONCLUSION: We describe here a novel, molecularly distinct CNS tumor class with strikingly variable histopathologic morphology. We postulate that the PATZ1 fusions are a key driver of tumor initiation. Preliminary indications suggest an intermediate prognosis.

OS12 RATIONALIZING COMBINATION PARTNERS OF IMMUNOTHERAPIES

OS12.4.A MHC CLASS II-RESTRICTED TRANSGENIC T CELL RECEPTOR THERAPY TARGETING MUTANT CAPICUA TRANSCRIPTIONAL REPRESSOR IN EXPERIMENTAL GLIOMAS

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BACKGROUND: Glioma subtypes are classified according to their characteristic mutations and show a high degree of resistance to standard therapeutic interventions such as radiotherapy and alkylating chemotherapy. Some of these characteristic mutations have shown to generate immunogenic neoepitopes that can be targeted with immunotherapy. 70% of oligodendrogliomas carry capicua transcriptional repressor (CIC) inactivating mutations. RESULTS: In a screen for potential immunogenic glioma neoepitopes we identified recurrent CIC hotspot mutations at position 215 (CICR215W/Q) expressed in a subset of oligodendrogliomas as an immunogenic major histocompatibility complex (MHC) class II-restricted neoepitopes. Peptide-based vaccination of MHC-humanized mice resulted in the generation of robust mutation-specific T cell responses against CICR215W/Q, restricted to MHC class II. Droplet-based single cell T cell receptor (TCR) sequencing from CICR215W-specific T cell lines enabled retrieval of MHC class II-restricted CICR215W-reactive TCRs. By retroviral transduction of T cells, we established a flow cytometry-based testing platform of retrieved TCRs and were able to show the top reactive TCR against CICR215W to be shared between individual mice. Using a newly developed glioma model in MHC-humanized mice induced by CRISPR-based delivery of tumor suppressor targeting guide RNAs, we show that adoptive intraventricular transfer of CICR215W-specific TCR-transgenic T cells exert anti-tumor responses against CICR215W-expressing syngeneic gliomas. CONCLUSION: The integration of immunocompetent MHC-humanized orthotopic glioma models in the discovery of shared immunogenic glioma neoepitopes facilitates the identification and preclinical testing of HLA-restricted neoepitope-specific TCRs for locoregional TCR-transgenic T cell adoptive therapy.

OS12.6.A COMBINATION THERAPY OF CAR-NK-CELLS AND ANTI-PD-1 RESULTS IN HIGH EFFICACY AGAINST ADVANCED-STAGE GLIOBLASTOMA IN A SYNGENEIC MOUSE MODEL AND INDUCES PROTECTIVE ANTI-TUMOR IMMUNITY IN VIVO

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INTRODUCTION: Checkpoint inhibitors as well as adoptive cell therapy hold promise for cancer therapy and encouraging treatment responses have already been demonstrated in different cancer indications. Glioblastoma (GB) is the most common and aggressive primary brain tumor. Standard therapy has very limited efficacy in the majority of patients. Analysis of the GB microenvironment (TME) has shown prominent immunosuppressive features, including expression of PD-L1 on tumor cells and increased frequency of FOXP3-positive regulatory T cells. While the surrounding brain is HER2-negative, GB are frequently HER2-positive, suggesting HER2 as a promising target for adoptive immunotherapy. Previous results from mouse glioma models showed efficacy of CAR-NK cells (NK-92/5.28.z) targeted against HER2 as monotherapy with early stage but not with advanced-stage tumors. MATERIALS AND METHODS: The murine glioma cell line GL261 was transfected with human HER2. Tumor cells were implanted either subcutaneously or orthotopically into C57BL/6 mice and treated either with HER2-specific NK-92/5.28.z cells alone or in combination with an anti-PD-1 antibody. Effects on tumor growth and survival were determined. Lymphocyte infiltration and immunosuppressive TME were characterized via highplex multi-color flow cytometry (FACS Symphony) and IHC (Phenoptics). Furthermore, gene expression profiles of tumor-infiltrating cells were determined via bulk RNAseq (NanoString). RESULTS: Combined treatment with NK-92/5.28.z cells and anti-PD-1 checkpoint blockade resulted in synergistic effects, with tumor regression and long-term survival observed even in advanced-stage tumor bearing mice. Analysis of the TME showed changes in lymphocyte infiltration and increased expression of exhaustion markers in tumor and immune upon combined treatment with NK-92/5.28.z cells and anti-PD-1 antibody resulting in an altered TME. Both, PD-1 and Lag-3 expression are highly upregulated on tumor infiltrating T cells. Total infiltrating lymphocytes show a rather cytotoxic phenotype up combination treatment with NK-92/5.28.z cells and anti-PD-1 antibody CONCLUSION: Our data demonstrate that efficacy of NK-92/5.28.z cells can be enhanced by combination with checkpoint blockade, resulting in successful treatment of advanced tumors refractory to NK-92/5.28.z monotherapy. Furthermore, the combination therapy induced a cytotoxic rather than immunosuppressive TME, leading to a primed immune system. To translate the concept of CAR-NK-cell therapy plus checkpoint inhibition to a clinical setting, we are adding a combination therapy cohort to our ongoing phase I clinical study (CAR2BRAIN; NCT03383978).

OS12.7.A CHARACTERIZATION OF INTRA-TUMORAL HETEROGENEITY AND DIFFERENTIAL IMMUNE ACTIVATION DURING MALIGNANT PROGRESSION OF MENINGIOMAS ON SINGLE CELL LEVEL

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BACKGROUND: As the most common intracranial tumor, meningiomas have caused increasing interest in the field of medical research. Based on their mutational profile, meningiomas can be separated into two main groups: NF2 altered meningiomas, which can occur at WHO grades 1 to 3, and non-NF2 mutant meningiomas with mutations in other genes, such as TRAF7, AKT1, KLF4, and SMO, which are usually of WHO grade 1. While this means that non-NF2 mutant meningiomas usually follow a benign course, risk stratification for NF2 mutant meningiomas remains difficult. As of now, the underlying mechanisms contributing to the malignant phenotype of some NF2 mutant