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Primary intracranial malignant melanoma (PIMM) is an uncommon cancer in childhood, that accounts for approximately 1% of melanoma, and 0.07% of brain tumors even in all age group. Because extracranial malignant melanoma usually occurs as a cutaneous lesion, affected patients have a chance to receive the early diagnosis and curable resection of the isolated tumor. However, unresectable metastatic cases have a poor prognosis with a median overall survival of 8 months. We report a 12-year-old girl with PIMM who received nivolumab therapy after an administration of dacarbazine. The tumor harbored no BRAF mutation. After the intravenous administration of nivolumab, cerebrospinal fluid 5-6-syntetin level declined and circulating CD8+HLA-DR+ cells increased, indicating the initial effect of nivolumab on PIMM. However, multiple lesions progressed for two month-immunotherapy, during which cerebrospinal fluid nivolumab concentrations attained to 1.2% of serum ones. The present case demonstrated the safety and modest effect of nivolumab for CNS melanoma. Nivolumab is a tolerable first-line therapy for diffuse PIMM, but pediatric patients need a more intensified CNS-specific immunotherapy.

IMMU-10. INTERIM ANALYSIS OF THE HIT-HGG REZ IMMUNVAC STUDY - DENDRITIC CELL VACCINATION WITH PARTIAL TREG DEPLETION IN CHILDREN, ADOLESCENTS, AND ADULTS WITH RELAPSED HIGH-GRADE GLIOMAS
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Efficacy of therapeutic dendritic cell vaccines (DCV) can be limited by immunomodulatory mechanisms in the microenvironment of high-grade gliomas. In the HIT-HGG-Rez Immunvac trial (Eudra-CT 2013-000419-26), we investigate whether a reduction of Treg with metronomic cyclophosphamide (metCyc) might be a feasible option to improve vaccine efficacy: 10 pediatric (mean age 11.4±4.2y) and 5 adult patients (mean age 19.5±19.9y) with relapsed glioblastoma were treated according to the HIT-HGG-Rez Immunvac protocol so far. 2 children were treated within the trial, the other 13 in the pilot phase. Patients received upfront oral metCyc for 2–4 weeks. After reoperation and monocye-apheresis, patients received 4 weekly intradermal injections of autologous, TDC+10 mL matured DCs, with tumor lysate in imiquimod-prepared skin. Thereafter, tumor lysate boostes were given. All patients received at least 5 vaccines (+4DCs, +1lysteae boostes). MetCyc was well tolerated and led to a reduction in Treg-frequency of 56.2% after cessation of metCyc administration. 13/14 analyzed patients showed a positive IFN-γ-Tcell response against autologous tumor lysate with a tendency to decrease over time. 6-month overall survival was 100%, compared to 65% in a historical control. Mean PFS of metCyc was 5.7 and 21.1 months with no difference between adults and children. We conclude that DCV in combination with partial Treg depletion is feasible, safe, and related with a high rate of tumor-specific IFNγ-responses. As the clinically and immunologically beneficial effects seem to be time consuming, we aim to combine our approach with checkpoint inhibition in the next amendment.

IMMU-11. LOCOREGIONAL DELIVERY OF TRANSIENT GD2 CAR T CELLS FOR SAFE AND EFFECTIVE TREATMENT OF DIPG
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Diffuse intrinsic pontine glioma (DIPG) is a universally fatal pediatric brain tumor with a median survival of one year. Recently Mount et al (Nat Med 2018) discovered the dasagluguoside G2D in present at high levels on the surface of DIPG and can be targeted using G2D-directed CAR T cells. However, permanently expressed CAR T cells created by lentiviral transduction resulted in a significant number of deaths from tumor swelling with uncontrolled T cell proliferation. We hypothesized that using mRNA to transiently express G2D-directed CAR T cells delivered locally with repeated dosing would result in a safer yet equally effective way to treat DIPG using CAR T cell therapy. In vitro studies using mRNA G2D-directed CAR T cells resulted in robust tumor cytokotoxicity and T cell degranulation across a panel of six DIPG cell lines. Using an orthotopic murine model of G2D-DIRX-dependent, an extremely aggres-
mm2 model, we delivered of a single dose of two million mRNA GD2-directed CAR T cells locoregionally to the pons via stereotactic injection. The mRNA GD2-directed CAR T cells resulted in no toxic deaths of the mice. In addition, a single dose of mRNA GD2 T-cells targeted GD2+ prolonged survival of the mice by a median of six days (p<0.05). Ongoing studies using an indwelling catheter for repeated dosing of mRNA CAR T cells are currently underway and results expected at the time of presentation. This work will form the basis of an mRNA CAR T cell trial targeting GD2 for patients with DIPG.

IMMU-12. PHASE I/II TRIAL OF IMMUNOTHERAPY WITH FUSIONS OF DENDRITIC CELLS AND TUMOR CELLS FOR RELAPSED OR REFRACTORY BRAIN TUMORS IN CHILDREN AND YOUNG ADULTS

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BACKGROUND/OBJECTIVES: Relapsed or refractory brain tumors in childhood continue to have a dismal prognosis in spite of intensive multi-disciplinary treatment. Cancer immunotherapy is newly developed to be expected as next promising treatment for highly aggressive pediatric cancer. This trial was designed to evaluate the safety and effectiveness of an immunotherapy with fusions of dendritic cells (DCs) and tumor cells in patients with relapsing or recurrent pediatric brain tumors. Methods: Pathologically confirmed malignant and recurrent/refractory brain tumors were eligible for this immunotherapy trial. Autologous cultured tumor cells obtained from surgical specimens were fused with autologous DCs using poly-ethylene glycol. The fusion cells (FC) were injected intradermally in the cervical region and repeated 3–10 times in each 28–84 days cycle. Treatment-related toxicity, progression-free survival (PFS), and overall survival (OS) were evaluated. RESULTS: Six patients were enrolled, three with high grade glioma and three with ependymoma. Median age at first course of immunotherapy was 10 years (range 8–25 years) and median follow-up time from the first course of immunotherapy was 13.5 months (range 3–33 months). All patients with immunotherapy were well tolerated to this treatment with no adverse events. Median progression free survival and overall survival were 18 months and 18.5 months, respectively. CONCLUSIONS: FC immunotherapy with autologous DCs and tumor cells for brain tumor in children and young adults were extremely well tolerated and showed encouraging responses in this series. Further phase II study of FC immunotherapy is planned to improve survival and reduce treatment related morbidity.

IMMU-13. DUAL IGF1R/IR INHIBITOR IN COMBINATION WITH GD2-CAR T-CELLS AS A POTENT THERAPEUTIC STRATEGY FOR H3K27M-MUTANT DIFFUSE MIDLINE GLIOMAS

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Diffuse midline gliomas (DMG) are aggressive pediatric brain tumors for which there is no effective treatment. Recent pre-clinical studies suggest that adoptive transfer of chimeric antigen receptor (CAR) T-cells targeting the disialoganglioside antigen GD2 (GD2-CAR) has a significant therapeutic potential. In this new linsitinib-GD2-CAR T-cell combination strategy in a DMG H3K27M-mutant 3D culture model. Our work supports the development of IGF1R/IR inhibitors to be used in combination with GD2-CAR T-cells for H3K27M-mutant DMG therapy.

IMMU-14. IMMUNE CHECKPOINT INHIBITOR THERAPY FOR TREATMENT OF SYNCHRONOUS CANCERS IN PAEDIATIC PATIENTS WITH CONSTITUTIONALMismatch REPAIR DEFICIENCY

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Constitutional mismatch repair deficiency (CMMRD) is an autosomal recessive condition in which affected patients carry biallelic germline mutations in the MMR genes. This highly penetrant syndrome results in nearly universal development of malignant neoplasms at a young age, most commonly pediatric brain tumors. In addition to brain tumors, patients frequently develop multiple metastatic or even synchronous tumors making it impossible to treat these cancers with current chemotherapeutic approaches due to the complexity of different chemoradiation regimens required, resulting in excess toxicity and lack of efficacy. We first, assessed the metachronous (defined here as serial tumors diagnosed >1 year apart or after completion of definitive treatment for the initial tumor) or synchronous cancers (defined here as tumors diagnosed within a year of each other or during the definitive treatment for the initial tumor) in all patients within the consortium. Strikingly, 47% developed synchronous and/or metachronous cancers leading to patient demise. Molecular analysis revealed that all synchronous tumors harbored a hypermutational burden accompanied by high genomic microsatellite instability and the relevant signatures. We therefore treated two patients with glioblastomas who had synchronous solid tumors with checkpoint inhibitors. In both patients, objective tumor response was associated with clinical benefit and prolonged survival. Biomarker analysis revealed increased tumor mutational burden, microsatellite instability and immune cell infiltration. These cases highlight the role of untargeted, mechanism based and tumor-agnostic approach to treat patients with brain tumors with additional synchronous cancers in the setting of cancer predisposition.

IMMU-15. PROTEOGENOMIC DISCOVERY OF NOVEL TUMOR PEPTIDES AS NEOAUTGENS FOR PERSONALIZED T CELL IMMUNOTHERAPY IN MEDULLOBLASTOMA BRAIN TUMORS

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T cell immunotherapies are promising new tools to combat high-risk subgroups of medulloblastoma without increasing the late effects burden. The ideal target antigen of an effective antitumor T-cell response is abundantly expressed by tumor cells but not by normal tissues, in order to limit off-target effects. Tumors translate a host of highly novel transcripts that are the result of aberrations in tumor DNA and the unmasking of alternative or novel exons. We developed a novel proteogenomic approach to identify tumor-restricted peptides and designed T-cell lines capable of mounting a tumor-specific cytotoxic immune response. Using RNA-seq and WGS data, we created personalized custom searchable databases containing predicted novel proteins from somatic mutations, novel junctions and fusion transcripts from 56 medulloblastoma tumors. By searching these databases with raw mass spectrometry data from paired medulloblastoma tumors, we identified tens of neoantigen peptides arising from the translation of tumor-specific transcripts; novel isoforms being the predominant class of tumor-specific peptides. Strikingly, 25% (p<0.0001) and 20% (p<0.0001) respectively, compared to GD2-CAR-T cells alone. The two compounds inhibited tumor cell proliferation through IGF1R/IR dependent mechanisms at a concentration which did not affect CAR T-cell expansion. Linsitinib, but not BMS-754807, decreased GD2-CAR-T cells and slowed their migration. Furthermore, linsitinib attenuated the expression of 10 out of 71 DMG genes involved in immunomodulation (e.g. IL33, VEGFC, STAT5A) and regulated upon tumorder CAR T-cells co-culture. Finally, we confirmed the anti-tumor activity of the new linsitinib-GD2-CAR T-cell combination strategy in a DMG H3K27M-mutant 3D culture model. Our work supports the development of IGF1R/IR inhibitors to be used in combination with GD2-CAR T-cells for H3K27M-mutant DMG therapy.