therapy (ipilimumab/nivolumab); two patients received monotherapy with either nivolumab or pembrolizumab. Median time from initial diagnosis-to-treatment was 8 months (range 0.8–136). Ten patients received radiation therapy (RT). RT and immunotherapy, given concurrently or as pre-treatment. RT. Median duration of treatment was 6.1 months (range 1–19). Therapy was discontinued in nine patients: seven due to disease progression and two due to adverse events (colitis, transaminits). Other pertinent toxicities included type 1 diabetes, hypothyroidism and skin toxicity. None of these toxicities were severe. Based on iRANO criteria, best responses included partial (n=4), stable (n=6) and progressive disease (n=1). Durable response (>12 months) was noted in two patients (HGG and progressive NGGCT). CONCLUSION: Immune checkpoint inhibition appears to have clinical benefit and is relatively well tolerated in this cohort of patients. Results from recently completed prospective clinical trials will be critical to inform clinical decisions.

IMMU-02. CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL NEUROTOXICITY CORRELATES WITH PRETREATMENT AND ACUTE CSF NEUROFILAMENT LIGHT CHAIN (NFL) LEVELS

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OBJECTIVE. Immune therapy for hematologic malignancies with CD19-directed CAR T cells is complicated by neurotoxicity in approximately 40% of patients. We have previously reported evidence of glial injury in pediatric patients with CAR T neurotoxicity by elevated CSF levels of GFAP and S100b. We now hypothesize that NFL is also a useful biomarker of neurotoxicity related to abnormal blood-brain-barrier and glial function. METHODS: We used the Mesoscale Discovery platform to measure CSF and serum NFL levels in a consecutive cohort of 43 pediatric patients with B cell ALL who received CD19-directed CAR T cells. In addition, we will present preliminary cohort measurements of NFL and GFAP (N=95). RESULTS: CSF NFL levels prior to CAR T cell infusion positively correlated with the risk of subsequently developing severe neurotoxicity (no neurotoxicity, median 273pg/mL; mild 378pg/mL; severe 951pg/mL; P=0.0182 for severe vs none, P=0.0458 for severe vs mild). During neurotoxicity, mean CSF NFL levels increased to 1179pg/mL (mild neurotoxicity, P=0.0338) and 1345pg/mL (severe neurotoxicity, P=0.0148), respectively. In serum, pretreatment NFL levels were highly abnormal in many patients (median 369pg/mL, range 10–56,320pg/mL; healthy control median 8pg/mL, range 1–7.5pg/mL). However, there was no correlation with neurotoxicity history of CNS radiation, peripheral neuropathy, stem cell transplant, or number of prior chemotherapies. Day 7 serum NFL levels did not change significantly (median 439pg/mL, range 5–7.4,393pg/mL, P=0.3254). CONCLUSION: NFL may be a biomarker of neurotoxicity after CAR T cell therapy. Further prospective studies are needed to establish NFL as an indicator of CAR T neurotoxicity risk and severity. The abnormal baseline serum NFL concentrations remain unexplained and require further study.

IMMU-03. UPDATES ON BRAINCHILD-01, -02, AND -03: PHASE 1 LOCOREGIONAL CAR T CELL TRIALS TARGETING HER2, EGFR, AND B7-H3 FOR CHILDREN WITH RECURRENT CNS TUMORS AND DIPG

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We report preliminary results of three Phase 1 trials of repetitively dosed locoregional CAR T cells for children with recurrent/refractory CNS tumors, targeting HER2 (BrainChild-01), EGFR (BrainChild-02), and B7-H3 (BrainChild-03). Cells are delivered into the tumor cavity (Arm A) or ventricular system (Arm B and BrainChild-03’s DIPG-specific Arm C). Primary endpoints are feasibility and safety. Successful CAR T cell manufacture occurred in 2/2 subjects (BrainChild-01) and 2/3 (BrainChild-02). All subjects tolerated intra-patient dose escalation from 1×10^6 to 2.5×10^6 cells/dose without DLTs. Two subjects were evaluable on BrainChild-01 (S-001: glioblastoma, Arm A, survival 173 days post-first infusion, received 6 infusions; S-002: ependymoma, Arm B, survival 111 days, 9 infusions). One subject was evaluable on BrainChild-02 (glioblastoma, Arm A, withdrew from trial at 49 days, 5 infusions). One enrolled patient on BrainChild-03 has not yet had repeat stimulation with B7-H3-CAR T cells. Despite the development of new neurologic toxicities, although transient worsening of baseline tumor-related signs and symptoms were seen. Secondary endpoints are efficacy and disease response. No objective radiographic responses have been observed. Both BrainChild-01 subjects had transient CRI elevations from baseline (peak of 3.9 post Course 1 Week 1; S-002: peak of 2.3 post Course 2 Week 1), possibly indicating an inflammatory response. Both subjects had post-infusion CSF cytocyte elevations (CXCL11, GCSF, GM-CSF, IFNα2, IFNγ, IL-10, IL-12p40, IL-12p70, IL-15, IL-1a, IL-6, IL-7, TNFa, VEGF) without concurrent systemic changes. In summary, we provide preliminary evidence of safety and feasibility of intracranial delivery of CAR T cells for pediatric CNS tumors.

IMMU-05. B7-H3-SPECIFIC CAR T CELLS HAVE POTENT ANTI-TUMOR ACTIVITY IN THE GL261 IMMUNE-COMPETENT MURINE BRAIN TUMOR MODEL

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BACKGROUND: We and others have identified B7-H3 (CD276) as a promising target for CAR-based immunotherapies for pediatric brain tumors. So far, B7-H3-CAR T cells have only been studied in xenograft models for brain tumors, which do not recapitulate the immunosuppressive tumor microenvironment (TME). Therefore, we set out to assess expression of B7-H3 on orthotopic GL261 glioma and its significance in the immune-competent GL261 murine glioma model which mimics human disease and host immune barriers. METHODS: To evaluate the safety and efficacy of antigen-specific CAR T cells, murine B7-H3-CAR T cells were generated using retroviral particles encoding 2nd generation B7-H3-specific CD28.x CAR. Expansion, persistence, and anti-tumor activity were evaluated in vitro and in vivo. Components of the brain TME were then evaluated using flow cytometry and immunostaining. RESULTS: B7-H3-CAR T cells targeted B7-H3+ tumor cells, secreted significant IL-2 and IL-10, IL12-p40, IL12-p70, IL-1a, IL-3, IL-6, IL-7, TNFa, VEGF) in an antigen-dependent manner and expanded an average of 33-fold in repeat stimulation assay with B7-H3+ tumor cells in contrast to control CAR T cells. In vivo, intratumoral injection of B7-H3-CAR T cells into orthotopic GL261 glioma induced complete regression in 60% of the mice. Preliminary studies show numerous infiltration of suppressive tumor-associated macrophages within the tumor and its periphery. CONCLUSIONS: In summary, we successfully generated murine B7-H3-CAR T cells and have demonstrated that these cells have potent anti-tumor activity in the immune-competent GL261 glioma model. However, it is likely that the tumor-associated macrophages are mediating immunosuppressive effects on B7-H3-CAR T cells. Therefore, studies focusing on TME/CAR T cell interactions are in progress.
of HLA class I suggests that pediatric brain tumors have developed immune evasion strategies to prevent recognition by conventional T cells.

**IMMU-07. IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY (ICANS) AMONG PEDIATRIC AND AYA PATIENTS: MD ANDERSON CANCER CENTER EXPERIENCE**

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**INTRODUCTION:** Immune effector cell associated neurotoxicity (ICANS) and cytokine release syndrome (CRS) are potentially life-threatening complications associated with immune effector cell (IEC) therapies. We characterize ICANS in pediatric and adult young adolescent (AYA) patients receiving IEC therapy at our institution. METHODS: We reviewed clinical characteristics and severity (based on ASCET Consensus Criteria) in pediatric and AYA patients with IEC products from 2018–2019 at MDACC. RESULTS: Nine patients, median age 15.5 (range: 3–25) years received chimeric antigen receptor (CAR) IEC therapy. Four (44%) developed ICANS within median of 8 (range: 3–27) days of CAR T cell infusion and median 6 (range: 2–7) days after CRS. Primary diagnoses were pre-B cell acute lymphoblastic leukemia (8) and mediastinal large B-cell lymphoma (1). Median CRS and ICANS severity grade was 2 (range 1–4). Symptoms included altered mental status (100%), aphasia (9), paresthesia (1), paresthesia (2), intracranial hypertension (1). Neuroimaging did not correlate to ICANS symptoms or severity. EEG was performed in 3 and 1 had background slowing correlating with aphasia. CSF was obtained in two revealing lymphocytosis. All received prophylactic anti-septic medication and tocilizumab for concomitant CRS. Three received steroids. CONCLUSION: ICANS may present in almost half of pediatric patients within one week of receiving CART products associated with CRS. CAR-T trafficking into the CSF may explain pleocytosis in the CSF. Prophylactic CAVE-1 may clarify. Impaired awareness may not be a normal limit.

**IMMU-08. REMATCH PROTOCOL: PHASE II STUDY OF EX-VIVO EXPANDED AUTOLOGOUS TUMOR SPECIFIC LYMPHOCYTE TRANSFER (X-ALT) + TOTAL TUMOR RNA DC vaccine (TT-RNA DC) FOLLOWING RECOVERY FROM PRIOR IMMUNOCHEMOTHERAPY (MAC) AND PERIPHERAL BLOOD STEM CELL (PBSC) RESCUE OR NON-MYELOABLATIVE CHEMOTHERAPY (NMAC) AND PBSC IN PATIENTS (PTS) WITH RECURRENT PNET (R-PNET)**

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A phase II study was performed to assess vaccine-related toxicities and efficacy of x-ALT+tr-RNA DC following MAC + PBSC (group A) or NMAC + PBSC (group B) in pts with r-PNET. METHODS: Eligible pts underwent chemotherapy to achieve complete remission and were then randomized to vaccine for vaccine-prepared pts with local (group A) or metastatic (group B) disease received cytokine in vivo vaccination chemotherapy prior to either MAC (carboplatin + thiopeta + etoposide) or NMAC (cyclophosphamide + fludarabine) respectively and then received one dose of x-ALT (3 x 10^7 cells/dose), PBSC, and 3 doses of bi-weekly intradermal tr-RNA DCs (10^6 cells each). Patients were followed for survival and vaccine-related toxicities. Correlative studies included TCR RNA sequencing and measurement of serum cytokines RESULTS: 20 evaluable pts (75% males [Medulloblastoma 17, PNET 3; unifocal 40%]); 20 evaluable pts (75% males [Medulloblastoma 17, PNET 3; unifocal 40%]). 16 patients were treated on protocol (group A 7, group B 13). There were no significant vaccine-related toxicities. At a median follow-up of 8.5 months, 5 patients (all with medulloblastoma) were alive following vaccine therapy; 2 pts with SD (3.5+ and 6.5+ months) and 3 pts with PD that stabilized with salvage therapies (26+, 31+, and 46+ months respectively). One patient with medulloblastoma and bone marrow involvement who had PD despite MAC, had an almost complete response one month following x-ALT + tr-RNA DCs and TCR RNA sequencing demonstrated massive clonal expansion of T cells. Correlative studies are ongoing CONCLUSIONS: x-ALT+tr-RNA DC following either MAC or NMAC is safe and shows signs of biologic and possible clinical activity in some pts with r-PNET.

**IMMU-09. NIVOLUMAB THERAPY FOR A PEDIATRIC-ONSET PRIMARY INTRACRANIAL MELANOMA**

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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, unresctable metastatic cases have a poor prognosis with an 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 showed a complete response in consensus criteria for 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 immunoregulatory 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 (metrCyc) might be a feasible option to improve vaccine efficacy. 10 pediatric (mean age 11.4±2.2y) and 5 adult patients (mean age 39.3±10.9y) 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 metrCyc for 2–4 weeks. After reoperation and monocye-apheresis, patients received 4 weekly intravenous doses of autologous, TNFa/IL-1ß matured DCs with tumor lysate in imiquimod-prepared skin. Thereafter, tumor lysate boostes were given. All patients received at least 5 vaccines (+4xDCs, 1xlystate boosts). MotrCyc was well tolerated and led to a reduction in Treg-frequency of 35.7±8.7% after a reduction of metrCyc dose of 1/2–7/3. 13/14 analyzed patients showed a positive IFNg-T-cell 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 and OS were 5.7±2.11 months with no difference between adult and children. We conclude that DCV in combination with partial Treg depletion is feasible, safe, and related with a high rate of tumor-specific IFNg-responses. As the clinically and immunologically beneficial effects seem to progress over time, we aim to combine our approach with checkpoint inhibition in the next amendment.

**IMMU-11. LOCCOREGIONAL 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 disialoganglioside GD2 is present at high levels on 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 (metrCyc) might be a feasible option to improve vaccine efficacy. 10 pediatric (mean age 11.4±2.2y) and 5 adult patients (mean age 39.3±10.9y) 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 metrCyc for 2–4 weeks. After reoperation and monocye-apheresis, patients received 4 weekly intravenous doses of autologous, TNFa/IL-1ß matured DCs with tumor lysate in imiquimod-prepared skin. Thereafter, tumor lysate boostes were given. All patients received at least 5 vaccines (+4xDCs, 1xlystate boosts). MotrCyc was well tolerated and led to a reduction in Treg-frequency of 35.7±8.7% after a reduction of metrCyc dose of 1/2–7/3. 13/14 analyzed patients showed a positive IFNg-T-cell 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 and OS were 5.7±2.11 months with no difference between adult and children. We conclude that DCV in combination with partial Treg depletion is feasible, safe, and related with a high rate of tumor-specific IFNg-responses. As the clinically and immunologically beneficial effects seem to progress over time, we aim to combine our approach with checkpoint inhibition in the next amendment.