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

Brandon Brown, Paolo Tambaro, Kris Mahadeo, Sajad Khazal, Priti Tewari, Demetrios Petropoulos, John Slopis, and Zsila Sadighi; The University of Texas at MD Anderson Cancer Center, Houston, TX, USA

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 ASTCT 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 (CART) 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 (AMS) (5), seizure (1), aphasia (2), impaired ability to write a standard sentence (4). 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-epileptic 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. Prospective studies may clarify. Impaired ability to write a standard sentence and the Cornell Assessment of Pediatric Delirium (CAPD) may be early indicators of ICANS in pediatric/AYA patients.

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) DURING RECOVERY FROM MYELOABLATIVE CHEMOTHERAPY (MAC) AND PERIPHERAL BLOOD STEM CELL (PBSC) RESCUE OR NON-MYELOABLATIVE CHEMOTHERAPY (NMAC) AND PBSC IN PATIENTS (PTS) WITH RECURRENT PNET (R-PNET)

Sridharan Gururangan[1,2], Eugene Hwang[3], Girish Dhall[4], Oleg Yegorov[1,5], Lance Governale[6,2], Jason Blatt[6,2], Biljana Horn[7,2], and Duane Mitchell[1,5]; [1]Preston A, Wells Center Jr. Center for Brain Tumor Therapy, Gainesville, FL, USA, [2]UF Health Shands Hospital, Gainesville, FL, USA, [3]Children's National Medical Center, Washington, DC, USA, [4]Children's Hospital of Alabama, Birmingham, AL, USA, [5]University of Florida, Gainesville, FL, USA, [6]Department of Neurosurgery, Gainesville, FL, USA, [7]Department of Pediatric Hematology-Oncology, Gainesville, FL, USA

A phase II study was performed to assess vaccine-related toxicities and efficacy of x-ALT+tt-RNA DC following MAC +PBSC (group A) or NMAC +PBSC (group B) in pts with r-PNET. METHODS: Eligible pts underwent biopsy to confirm r-PNET and obtain tumor for vaccine preparation. Pts with local (group A) or metastatic (group B) disease received cytoreductive induction chemotherapy prior to either MAC (carboplatin+ thiotepa+ etoposide) or NMAC (cyclophosphamide + fludarabine) respectively and then received one dose of x-ALT (3 x 10^7cells/kg), PBSC, and 3 doses of bi-weekly intradermal tt-RNA DCs (10^7cells 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%] 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) are 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 + tt-RNA DCs and TCR RNA sequencing demonstrated massive clonal expansion of T cells. Correlative studies are ongoing CONCLUSIONS: x-ALT+tt-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

Utako Oba[1], Yuhki Koga[1], Riichiro Kawaguchi[1], Kentaro Nakashima[1], Yojiro Akagi[2], Nobuhiro Hata[2], Nanae Yamamoto[3], Kenichi Kohashi[4], Satohiro Masuda[3], Koji Iihara[2], Yoshinao Oda[4], and Shouichi Ohga[1]; [1]Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [2]Department of Neurosurgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [3]Department of Pharmacy, Kyushu University Hospital, Fukuoka, Japan, [4]Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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-S-cysteinyldopa levels declined and circulating $CD8^+HLA\text{-}DR^+$T 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

Matthias Eyrich[1], Jürgen Krauss[2], Johannes Rachor[1], Camelia Monoranu[3], Brigitte Bison[4], Mario Löhr[2], Stefan Rückriegel[2], Matthias Wölfl[1], Elisabeth Miller[1], Paul G Schlegel[1], and Christof Kramm[5]; [1]University Children's Hospital, Würzburg, Germany, [2]Dep. Neurosurgery, Würzburg, Germany, [3]Dep. Neuropathology, Würzburg, Germany, [4]Dep. Neuroradiology, Würzburg, Germany, [5]University Children's Hospital, Göttingen, Germany

Efficacy of therapeutic dendritic cell vaccines (DCV) can be limited by immunosuppressive mechanisms in the micromilieu of high-grade gliomas. In the HIT-HGG-Rez Immunovac 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±4.2y) and 5 adult patients (mean age 39.5±19.9y) with relapsed glioblastoma were treated according to the HIT-HGG-Rez Immunovac 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 monocyte-apheresis, patients received 4 weekly intradermal doses of autologous, TNFa/IL-1ß matured DCs pulsed with tumor lysate in imiquimod-prepared skin. Thereafter, tumor lysate boosts were given. All patients received at least 5 vaccines (4xDCs, 1xlysate boosts). MetrCyc was well tolerated and led to a reduction in Treg-frequency of 35.6±17.8% followed by a rebound after cessation of metrCyc. Importantly, 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 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 IFNg-responses. As the clinically and immunologically beneficial effects seem to diminish over time, 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

Jessica Foster, Crystal Griffin, Allison Stern, Cameron Brimley, Tiffany Smith, Phillip Storm, and Adam Resnick; Children's Hospital of Philadelphia, Philadelphia, PA, USA

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 the surface of DIPG and can be targeted using GD2-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 create transient GD2-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 GD2-directed CAR T cells resulted in robust tumor cytotoxicity and T cell degranulation across a panel of six DIPG cell lines. Using an orthotopic murine model of SU-DIPGXIIIP*, an extremely aggres-

sive 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 CAR T cells targeting 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 of 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

Masayoshi Yamaoka[1], Yasuharu Akasaki[2], Jun Takei[2], Masaharu Akiyama[1], Tetsunori Tasaki[3], Toya Ohashi[4], Hiroyuki Ida[1], and Takaaki Yanagisawa[2]; [1]Jikei University School of Medicine, Pediatrics, Tokyo, Japan, [2]Jikei University School of Medicine, Neurosurgery, Tokyo, Japan, [3]Jikei University School of Medicine, Blood transfusion and cell therapy, Tokyo, Japan, [4]Jikei University School of Medicine, Gene therapy, Tokyo, Japan

BACKGROUND/OBJECTIVES: Relapsed or refractory brain tumors in childhood continue to have a dismal prognosis in spite of intensive multidisciplinary 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 malignant brain tumors. METHODS: Patients with histopathologically confirmed malignant and recurrent/refractory brain tumor were eligible for this immunotherapy trial. Autologous cultured tumor cells obtained from surgical specimens were fused with autologous DCs using polyethylene glycol. The fusion cells (FC) were inoculated 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 except local erythema in injected site. 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

Emmanuel de Billy[1], Marsha pellegrino[1], Biagio De Angelis[1], Pietro Businaro[1], Domenico Orlando[1], Giulia Pericoli[1], Lucia Lisa Petrilli[1], Sabrina Rossi[2], Roberta Ferretti[1], Nicola Maestro[1], Luca Massimi[3], Marco Pezzullo[4], Cristiano De Stefanis[4], Rossella Rota[1], Francesco Ferrari[5,6], Elisa Salviato[5], Andrea Carai[7], Ignazio Caruana[1], Franco Locatelli[1,8], Angela Mastronuzzi[9], Concetta Quintarelli[1], and Maria Vinci[1]; [1]Department of Paediatric Haematology and Oncology, Cellular and Gene Therapy, Bambino Gesù Children's Hospital-IRCCS, Rome, Italy, [2]Department of Laboratories, Pathology Unit, Bambino Gesù Children's Hospital-IRCCS, Rome, Italy, [3]Pediatric Neurosurgery, Department of Neurosurgery, Fondazione Policlinico Gemelli-IRCCS, Rome, Italy, [4]Research Laboratories, Bambino Gesù Children's Hospital-IRCCS, Rome, Italy, [5]IFOM, the FIRC Institute of Molecular Oncology, Milano, Italy, [6]CNR Institute of Molecular Genetics "Luigi Luca Cavalli-Sforza", Pavia, Italy, [7]Oncological Neurosurgery Unit, Department of Neuroscience and Neurorehabilitation, Bambino Gesù Children's Hospital-IRCCS, Rome, Italy, [8]Department of Gynaecology/Obstetrics and Paediatrics, Sapienza University of Rome, Rome, Italy, [9]Neuro-oncology Unit, Department of Paediatric Haematology and Oncology, Cellular and Gene Therapy, Bambino Gesù Children's Hospital-IRCCS, Rome, Italy

Diffuse midline gliomas (DMG) are aggressive paediatric 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 for H3K27M-mutant DMG. Still, some tumor cells resist to treatment suggesting that a multimodal approach may be necessary to treat more efficiently the disease. Our aim was to identify chemical compounds that, in combination with CAR T-cells, would enhance anti-tumor efficacy. After having confirmed the GD2 expression in tissue samples and patient-derived H3K27M-mutant DMG cells, we developed a high throughput cell-based assay to screen 40 kinase inhibitors in combination with T-cells expressing the GD2-CAR.CD28.4-1BB.z construct. The screening led to the identification of the dual IGF1R/IR antagonists, BMS-754807 and linsitinib, which, in combination with GD2-CAR T-cells, improved antitumor activity by 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 exhaustion and increased their memory profile. Furthermore, linsitinib attenuated the expression of 10 out of 71 DMG genes involved in immunomodulation (*e.g.* IL33, VEGFC, STAT5A) and regulated upon tumor/CAR T-cells co-culture. Finally, we confirmed the anti-tumor activity of the new linsitinib/GD2-CAR T-cells 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 PAEDIATRIC PATIENTS WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY

Jacob Henderson[1], Daniel Morgenstern[2], Melissa Edwards[2], Sumedha Sudhaman[2], David Kram[3], Michael Osborn[4], Yoon-Jae Cho[5], and Uri Tabori[2]; [1]Mary Bridge Children's Hospital, Tacoma, WA, USA, [2]Hospital for Sick Children, Toronto, ON, Canada, [3]Wake Forest School of Medicine, Winston Salem, NC, USA, [4]Royal Adelaide Hospital, Adelaide, Australia, [5]Oregon Health and Science University, Portland, OR, USA

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. Importantly, in addition to brain tumors, patients frequently develop multiple metachronous 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 (n=26) 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 universal, 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 NEOANTIGENS FOR PERSONALIZED T CELL IMMUNOTHERAPY IN MEDULLOBLASTOMA

Samuel Rivero-Hinojosa, Melanie Grant, Aswini Panigrahi, Huizhen Zhang, Veronika Caisova, Catherine Bollard, and Brian Rood; Children's National Research Institute, Washington, DC, USA

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 used them to select and expand T cells 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 source. We tested these peptides for their ability to select and expand autologous polyclonal populations of T cells and tested the immunogenicity of each individual peptide. Flow cytometry revealed populations of CD4+ and CD8+ cells with an activation profile marked by IFN-γ and TNF-α. Immunosuppressive marker profiles were also characterized. Using cytotoxicity assays, we demonstrated that tumor specific T cells can eliminate neoantigen bearing tumor cells. Thus, proteogenomics can identify immunogenic tumor