Title

CTIM-32. PHASE II AND BIOMARKER STUDY OF PEMBROLIZUMAB OR PEMBROLIZUMAB PLUS BEVACIZUMAB FOR RECURRENT GLIOBLASTOMA PATIENTS

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Authors

Reardon, David
Molinaro, Annette
Peters, Katherine
et al.

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survival. Pituitary carcinomas recur despite conventional multimodality treatments. Given the recent advances in the use of immune checkpoint inhibitors (CPIs) to treat various solid cancers, there is interest in exploring the role of immunotherapy for treating aggressive, refractory pituitary tumors. We treated four pituitary carcinoma patients with pembrolizumab as part of a phase II clinical trial (NCT02721732). Here, we present their clinical course and outcomes and correlate responses with available molecular data: hypermutation status, PD-L1 staining, tumor-infiltrating lymphocyte score, microsatellite status and tumor mutational burden. Patients 1 and 2, with heavily pretreated, refractory corticotroph pituitary carcinoma, had partial radiographic (60% and 32% per irRECIST, respectively) and hormonal responses. Patient 1's response continues 42 months after initiation of pembrolizumab and his baseline tumor tissue obtained after treatment with temozolomide demonstrated a hypermutator phenotype with *MSH2* and *MSH6* gene mutations. Patient 2's tumor was not sampled after exposure to temozolomide, but prior somatic mutational testing was negative. Patient 3 (non-functioning corticotroph tumor) had a best response of stable disease for four months. Patient 4 (prolactin-secreting carcinoma) had progressive disease. The latter two patients' tumors did not demonstrate a hypermutator phenotype after treatment with temozolomide. PD-L1 staining was negative in all tumors. TIL score was 2 in Patients 1 and 4, negative in Patient 3 and not available in Patient 2. All patients tolerated the treatment well with mild adverse events. Our study generates the hypothesis that an alkylating agent-induced hypermutator phenotype may be an indicator of response to CPIs in pituitary carcinomas. The role of CPI in treating patients with pituitary carcinoma and mechanisms of hypermutation in this population require further study.

CTIM-31. USE OF A SINGLE PEPTIDE CHECKPOINT INHIBITOR FOR TREATMENT OF CENTRAL NERVOUS SYSTEM TUMORS

Christopher Moertel[1], Zhengming Xiong[1], David Zellmer[1], Elizabeth Pluhar[2], Elizabeth Neil[1], Emely Greengard[1], and Michael Olin[1]; [1]University of Minnesota, Minneapolis, MN, USA, [2]University of Minnesota, St. Paul, MN, USA

Cancer immunotherapy has revolutionized clinical management of malignancies by generating long-term, durable control of tumors. Unfortunately, these therapies often cause serious immune-related adverse events. In addition, only a small percentage of solid tumors respond to these therapies and there is little efficacy in CNS tumors. Our research is focused on the CD200 immune checkpoint, which modulates the immune system through the inhibitory receptor (CD200R1) and activation receptors (CD200AR). We demonstrated that targeting the CD200AR with a checkpoint peptide ligand (CD200AR-L) activates the immune system and renders it impervious to the inhibitory effects of CD200. In a pre-clinical canine spontaneous high-grade glioma trial, CD200AR-L, with autologous tumor lysate vaccination, resulted in a 20% two-year progression-free survival; no toxicities or adverse effects were observed. We suggest this result was due to the ability of the CD200AR-L to modulate multiple immune checkpoints. During the characterization of the CD200AR-L, we discovered signaling molecules are shared by the CD200 and PD-1/PD-L1 checkpoint pathways, suggesting these immune checkpoints are connected. Our preliminary studies demonstrated that the inhibitory CD200R1 and PD-1 mediate immune checkpoint signaling activities through the SHIP1/2. Moreover, CD200AR-L overpowers the suppressive effects of CD200 and PD-L1, which are both shed by tumors, by downregulating the inhibitory CD200R1 and PD-1 on both antigen-presenting cells (**APC**) and T-cells. In addition, CD200AR-L downregulates PD-1 on APCs and inhibits the upregulation of PD-L1 and CTLA4. These studies led to the discovery that the novel peptide modulates the CD200, PD-1/PD-L1 and CTLA-4 pathways, providing the basis for the translatable development of a CD200-directed peptide for clinical use against multiple tumors including gliomas. These studies led to FDA approval of this peptide for the first in human phase I single center, open-label, dose-escalation clinical trial in adult and pediatric trial for children with recurrent malignant brain tumors.

CTIM-32. PHASE II AND BIOMARKER STUDY OF PEMBROLIZUMAB OR PEMBROLIZUMAB PLUS BEVACIZUMAB FOR RECURRENT GLIOBLASTOMA PATIENTS

David Reardon[1], Annette Molinaro[2], Katherine Peters[3], Jennifer Clarke[2], Justin Jordan[4], John de Groot[5], Phioanh Nghiemphu[6], Thomas Kaley[7], Howard Colman[8], Christine McCluskey[9], Timothy Smith[10], David Cote[11], Mariano Severgnini[9], Jennifer Yearley[12], Qing Zhao[12], Wendy Blumenschein[12], Gabriel Duda[13], Alona Muzikansky[4], Rakesh Jain[14], Patrick Wen[15], and Lakshmi Nayak[15]; [1]Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [2]Department of Neurological Surgery, University of California (UCSF), San Francisco, San Francisco, CA, USA, [3]Duke University Medical Center, Durham, NC, USA, [4]Massachusetts General Hospital, Boston, MA, USA, [5]University of Texas MD Anderson Cancer Center, Houston, TX, USA, [6]University of California Los Angeles, Los Angeles, CA, USA, [7]Memorial Sloan Kettering Cancer Center, NYC, NY, USA, [8]Huntsman Cancer Institute, Salt Lake City, UT, USA, [9]DFCI, Boston, MA, USA, [10]Department of Neurosurgery, Brigham and Women's Hospital, Boston, MA, USA, [11]BWH, Boston, MA, USA, [12]Merck, Kenilworth, USA, [13]MGH, Boston, MA, USA, [14]Edwin L. Steele Laboratories, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, [15]Dana-Farber Cancer Institute, Boston, MA, USA

PURPOSE: Vascular endothelial growth factor (VEGF) is upregulated in glioblastoma and may contribute to immunosuppression. We performed a phase 2 study of pembrolizumab, a programmed death-1 (PD-1) blocking antibody alone or with the anti-VEGF antibody bevacizumab in recurrent glioblastoma with detailed analyses of biomarkers and patient neurologic function. METHODS: Eighty bevacizumab-naive, recurrent glioblastoma patients were randomized to receive pembrolizumab with bevacizumab (cohort A, n=50) or pembrolizumab monotherapy (cohort B, n=30). The primary endpoint was six-month progression-free survival (PFS-6). Exploratory endpoints included evaluation of tumor PD-L1 expression, TIL density, immune activation gene expression signature and plasma cytokines with outcome. Changes in neurologic function were prospectively assessed using the Neurologic Assessment in Neuro-Oncology (NANO) scale. RESULTS: Pembrolizumab alone or with bevacizumab was well tolerated but of limited benefit. For cohort A, PFS-6 was 26.0% (95% CI: 16.3, 41.5), median OS was 8.8 months (95% CI: 7.7, 14.2), ORR was 20% and median duration of response was 48 weeks. For cohort B, PFS-6 was 6.7% (95% CI: 1.7, 25.4), median OS was 10.3 months (95% CI: 8.5, 12.5) and ORR was 0%. Factors associated with worsened OS included baseline dexamethasone use and increased post-therapy plasma VEGF (cohort A) and wild-type *IDH1*, unmethylated *MGMT* and increased baseline PlGF and sVEGFR1 levels (cohort B), but tumor immune markers were not informative. The NANO scale effectively predicted neurologic function. CONCLUSIONS: Although well tolerated, pembrolizumab was ineffective both as monotherapy and with bevacizumab for recurrent glioblastoma. Nonetheless, radiographic responses to combinatorial therapy were durable. Baseline dexamethasone use and plasma cytokines but not tumor immunologic biomarkers were associated with outcome. Neurologic function evaluated by the NANO scale contributed to outcome assessment.

CTIM-33. THE REMIND TRIAL: MULTI-ANTIGEN TARGETED T CELLS FOR PEDIATRIC CNS TUMORS

Melanie Grant[1], Maria Fernanda Fortiz[2], Jennifer (Lu) Wang[2], Haili Lang[2], Anushree Datar[2], Emily Reynolds[2], Madeline Terpilowski[2], Christopher Lazarski[2], Jay Tanna[2], Adriana Pitino[2], Nan Zhang[2], Fahmida Hoq[2], Patrick Hanley[2], Lindsay Kilburn[2], Roger Packer[2], Brian Rood[2], Catherine Bollard[2], and Eugene Hwang[2]; [1]Children's National Hospital, Silver Spring, MD, USA, [2]Children's National Hospital, Washington, DC, USA

BACKGROUND: Patients with relapsed CNS malignancies or DIPG face terrible prognoses. We hypothesized that T cells specific for 3 tumor-associated antigens (TAA), WT1, PRAME and survivin, would be safe and elicit anti-tumor immunity. METHODS: Patients (n=15) received autologous tumor antigen-associated T cells (TAAT) (up to $4x10^7/m^2$) for newly diagnosed DIPG (Group A) or recurrent CNS malignancies (Group B) on a Phase I dose-escalation study (NCT03652545) and were monitored for safety and response. RESULTS/DISCUSSION: 15/15 patients who received TAAT completed the 45-day safety monitoring phase with no dose-limiting toxicities. Adverse events were minimal despite multiple pretreatments in Group B. Infused cells were predominantly CD3+ T cells (median 96%; range: 87–99%), with CD4+ and CD8+ comprising 16% (range: 5–87%) and 40% (range: 4–67%) respectively. Specificity for 1–3 TAAs was demonstrated in 13/15 TAAT by a-IFN-γ ELISPOT. Plasma cytokine and proteomic analyses are ongoing but have demonstrated dynamic post-infusion immune cytokine and protein responses. Increases in the inflammatory and immune-stimulatory cytokines IL-1b, IL-6, IL-2 and IL-7 were observed post-infusion in most patients evaluated. Infusion-related increases in regulatory cytokines IL-10 and IL-13 were also observed in 4/7 patients. These results are consistent with an infusion-mediated immune response in vivo. Of 9 patients who have been tested thus far, 29/92 plasma proteins showed significant differences between dose levels 1 and 2, including increased IL-7 ($p < 0.0004$) and CD40L ($p < 0.046$) and reduced IL-4 ($p < 0.0004$). T cell receptor sequencing data on in vivo TAAT persistence is pending. In summary, TAAT have thus far been safe and elicit immune responses in vivo. Clinical and immunologic response assessments are ongoing.

CLINICAL TRIALS: NON-IMMUNOLOGIC

CTNI-01. EFFECT OF STEREOTACTIC RADIOSURGERY COMPARED TO WHOLE-BRAIN RADIOTHERAPY FOR LIMITED BRAIN METASTASIS ON LONG TERM COGNITION AND QUALITY OF LIFE: A POOLED ANALYSIS OF RANDOMIZED CLINICAL TRIALS

Joshua Palmer[1], Brett Klamer[2], Karla Ballman[3], Paul Brown[4], Jane Cerhan[4], S. Keith Anderson[4], Anthony Whitton[5], Jeffrey Greenspoon[5],