dritic cell (DC) vaccination in small clinical trials. In this Phase II clinical trial, we randomized malignant glioma patients to receive autologous tumor lysate pulsed DC vaccination with and without adjuvant toll-like receptor (TLR) agonists. Treatment with TLRs in cancer patients has been shown to activate the innate immune response by inducing the expression of pro-inflammatory factors and cytokines. Twenty-three patients with WHO grade III or IV glioma received three intradermal injections of autologous tumor lysate-pulsed DC on days 0, 14, and 28 in conjunction with either a placebo adjuvant, TLR-7 agonist (Resiquimod), or TLR-3 agonist (Poly ICLC). We observed a difference in survival for the DC-vaccinated patients who received adjuvant Poly ICLC treatment of 54 months over adjuvant placebo (20 months) and adjuvant Resiquimod (28 months) groups (P = 0.04). The patient cohorts were balanced for WHO grade, IDH mutation, and MGMT methylation status. Mass cytometry (CyTOF) analysis of patient peripheral blood mononuclear cells (PBMCs) showed increased levels of the monocyte populations CD14+CD16- and CD14dimCD16+ after Poly ICLC treatment. In addition, gene expression analysis of the PBMC populations using single cell RNA sequencing demonstrated increased expression of pro-inflammatory genes after adjuvant Poly ICLC and Resiquimod treatment. Nonetheless, a greater fold change increase and a larger pro-inflammatory repertoire was observed in the Poly ICLC group. Overall, these findings demonstrate that adjuvant Poly ICLC increases the number of circulating monocytes and induces a large pro-inflammatory response, which may account for the survival differences observed over adjuvant Resiquimod and placebo.

CTIM-19. MOLECULAR AND GENETIC DETERMINANTS OF RESPONSE TO PD-1 BLOCKADE IN RECURRENT GLIOBLASTOMA PATIENTS

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Despite immune checkpoint inhibitors having success in several other tumor types, many glioblastoma (GBM) patients fail to respond or maintain a sustained response. Work published by our group (Cloughesy *et al*, 2019) demonstrated that relative to adjuvant programmed cell death-1 (PD-1) blockade, neoadjuvant treatment doubled the median overall survival (OS) for recurrent GBM patients and resulted in an enhanced interferon-γ signature. This suggests that anti-PD-1 given in the neoadjuvant setting may improve outcomes for recurrent GBM patients. The challenge remains in identifying the molecular and genetic signatures associated with response to immune checkpoint blockade. To address this, we analyzed the tumor sample and clinical response data from the patients treated in this clinical trial (n=31). We stratified patients as stable disease (SD) versus progressive disease (PD) based on their response assessment in neuro-oncology criteria (RANO) scores from cycle 2 of treatment post-surgery. Among the SD patients, 77.8% received neoadjuvant treatment while 22.2% received adjuvant therapy. In this group, a median OS was not reached. Among the PD patients, 40.9% received neoadjuvant treatment and 59.1% received adjuvant therapy, with a median OS of 257 days. Next, we analyzed factors that impact response to immunotherapy, which includes somatic mutational burden and interferon-γ pathway induction. We calculated somatic mutational variants, copy number variants (CNVs), and differential gene expression from the bulk tumor exome and RNA-sequencing data. The total mutation counts were similar between groups and no association was identified with increased mutational burden. In addition, total CNV stability was similar between groups. However, when looking at genes involved in the JAK/STAT signaling pathway, there were notably more copy number losses of JAK2 in the PD group when compared to the SD group (85.0% versus 66.7%). These findings merit further exploration as the JAK/STAT pathway has been implicated in response to immune checkpoint blockade.

CTIM-20. PHASE I STUDY OF IBRUTINIB WITH RADIATION AND TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

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BACKGROUND: Glioblastoma is a devastating disease that is notoriously resistant to current therapies, leading to dismal patient outcomes and a median survival of just 14.6 months. A major problem in glioblastoma treatment is the inability to effectively target the cell population that gives rise to recurrence. These cells, known as glioma stem cells (GSCs) or tumor propagating cells are endowed with a large capacity for self-renewal to propagate the tumor. GSCs are resistant to radiation. Ibrutinib is a first-in-class, potent, orally administered, covalently binding Inhibitor of Bruton's Tyrosine Kinase (BTK). Ibrutinib is a small-molecule tyrosine kinase. It also inhibits BMX. Bone marrow X-linked (BMX) nonreceptor tyrosine kinase activates STAT3 signaling to maintain self-renewal and tumorigenic potential of GSCs. Hence a combination of ibrutinib with radiation and or temozolomide in patients with newly diagnosed Glioblastoma is warranted. METHODS: This is a two arm study. Arm 1 is for patients with unmethylated MGMT Glioblastoma. Every patient gets ibrutinib and 60 Gy radiation over 6 weeks. Patients will undergo a 4-week break and Ibrutinib treatment will then continue until disease progression, intolerable toxicity or death. Arm 2 is for patients with MGMT methylated glioblastoma. Every patient will receive Ibrutinib and 60 Gy radiation and daily Temozolomide at 75 mg/m2 for 6 weeks. Patients will undergo a 4-week break then receive daily ibrutinib and adjuvant Temozolomide. The temozolomide will continue until disease progression, intolerable toxicity or death or maximum of 6 cycles. Ibrutinib treatment will continue until disease progression, intolerable toxicity or death. RESULTS: The maximum tolerated dose (MTD) of Ibrutinib with radiation (2 Gy x 30) in patients in each arm will be reported. The safety of Ibrutinib with radiation and with radiation and temozolomide will be reported. The Progression free survival and overall survival in each arm will be reported. CONCLUSION: This is an ongoing clinical trial. Results will be reported once study is complete.

CTIM-21. PEPTIDE VACCINE DIRECTED TO CMV PP65 FOR TREATMENT OF RECURRENT MALIGNANT GLIOMA AND MEDULLOBLASTOMA IN CHILDREN AND YOUNG ADULTS: PRELIMINARY RESULTS OF A PHASE I TRIAL

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INTRODUCTION: The cytomegalovirus (CMV) antigen, pp65, is ubiquitously expressed in malignant glioma and medulloblastoma but not in healthy brain. The objective of this Phase I trial (NCT03299309) was to assess the safety and feasibility of a novel pp65 peptide vaccine (PEP-CMV) in children and young adults with recurrent medulloblastoma and malignant glioma. METHODS: Vaccines contain a synthetic long peptide (SLP) of 26 amino acids encoding multiple potential class I, class II, and antibody epitopes of CMV pp65 across several haplotypes. This SLP is administered as an emulsion in Montanide ISA 51. Patients receive a single course of temozolomide to induce lymphopenia, tetanus/diphtheria toxoid site preconditioning, then vaccines administered intradermally every two weeks for 3 doses, then monthly. RESULTS: To date, 17 patients have been enrolled. Diagnoses include medulloblastoma (n=1), glioblastoma (n=9), anaplastic oligodendroglioma (n=2), anaplastic astrocytoma (n=2), and malignant glioma NOS (n=3). Mean number of prior treatment regimens is 4.9 (range 1–12). Mean age is 22yo (range 6–35) and 41% of patients are male. The median KPS is 80. The median number of vaccines given at time of analysis is 3.3 (range 1–12). There have been no ≥ 3 Grade toxicities related to the vaccine. One patient developed nausea, vomiting, palpitations, and tachycardia after vaccination and had elevated inflammatory cytokines consistent with cytokine release syndrome. Median PFS is 2.5 months (95% CI: 0.8, not estimable) and median OS is 6.5 months (95% CI 1.8, not estimable). Interim analysis of immune monitoring bloodwork and perfusion MRI to quantify responses to PEP-CMV has been delayed due to COVID-19. However, adults with GBM who received PEP-CMV (NCT02864368) had significant ($p \leq 0.05$) increases in GCSF, GM-CSF, IFN-γ, IL-10, IL-2, IL-8, MIP1-α, and TNF-α levels. CONCLUSIONS: Preliminary results demonstrate that PEP-CMV is feasible and well-tolerated in heavily pretreated, multiply recurrent patients.

CTIM-22. PHASE 1 TRIAL OF OSIMERTINIB WITH STEREOTACTIC RADIOSURGERY (SRS) IN PATIENTS WITH BRAIN METASTASES FROM EGFR POSITIVE NON-SMALL-CELL LUNG CANCER (NSCLC)

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BACKGROUND: Osimertinib is an oral, irreversible inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor activating mutation (EGFRm) and the resistance mutation (T790M) that is FDA approved for patients with EGFR mutant lung cancer. The synergism between Osimertinib and radiation likely enhances DNA damage, leading to increased cell apoptosis. For patients with EGFR positive NSCLC with brain