Title

CTIM-09. DOUBLE-BLINDED, PLACEBO CONTROLLED PHASE 2 STUDY OF ERC1671 IN RECURRENT GLIOBLASTOMA: VACCINE OVERALL SURVIVAL IN BEVACIZUMAB NAIVE AND BEVACIZUMAB RESISTANT PATIENTS

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(OS) 14 months and 5-year survival rate of under 10%. Dendritic cells (DCs) are the professional antigen presenting cells of the immune system. The rationale for sensitizing dendritic cells to a pool of non-selected tumor antigens is based on the marked heterogeneity present within glioblastoma tumor cells. METHODS: Phase 1/feasibility study of DC vaccine for recurrent high-grade glioma was conducted. Pooled, non-selected tumor antigens collected via tumor cell lysate were used for DC sensitization. RNA sequencing analysis was performed on all tumor samples. Cytokine levels in serum were detected using a Luminex cytokine panel. RESULTS: A total of 20 patients were enrolled onto this study (median age 58yrs, range: 39–74, 65% male). Pathology showed WHO grade IV glioblastoma in 14 (70%) and grade III anaplastic astrocytoma in 6 (30%) patients. IDH wild type in 19 (95%) patients. Treatment emergent adverse events (all grades, regardless of attribution) occurred in more than 15% of the patients (20% fatigue, 15% dizziness, 15% headache, none leading to treatment discontinuation). There were five grade 3–4 and none grade 5 events. One grade 4 event (seizure) probable related to investigational treatment leading to treatment discontinuation. Four grade 3 events (dysphasia, possible related; intracranial hemorrhage unrelated; muscle weakness, unlikely related and hematoma, unrelated). Median PFS was 3.8 months. Median OS was 11 months. RNA sequencing in tumor samples and correlation with cytokine levels in serum is currently been analyzed. CONCLUSION: Tumor lysate pulsed DC vaccination demonstrates acceptable safety and tolerability in high-grade glioma patients. Evaluations of integrating molecular profiling RNA sequencing information and cytokine levels to identify potential subset of patients with significant clinical benefit will be provided.

CTIM-07. IDENTIFICATION OF A BASELINE BIOMARKER ASSOCIATED WITH TUMOR RESPONSES IN A PHASE I/IIA TRIAL OF A THERAPEUTIC CMV VACCINE AGAINST RECURRENT GLIOBLASTOMA (GBM)

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Cytomegalovirus (CMV) antigens have been reported in over 90% of GBM tumors. $CD4^+$ and $CD8^+$ T cells are most frequently directed against the gB and pp65 antigens, respectively, and are immunogenic targets in a CMV-based GBM vaccine. We enrolled 10 patients (6 women, 4 men) with KPS at least 70 and first recurrence of GBM to a trial (Phase IIa extension) of gB/pp65 enveloped virus-like particles (eVLPs) with GM-CSF. Intradermal vaccination was administered every 4 weeks, with serologic immune-monitoring 2 weeks after each vaccination and surveillance brain MRI scans every 6 weeks. Median age was 59 years (range 33–67). Among 8 response-evaluable patients, we observed 1 SD and 1 PR. Among all patients treated on phase I and II (n=26), a normal baseline ratio of CD4/CD8 T cells in peripheral blood predicted response (n=6). Other baseline peripheral blood markers did not correlate with efficacy, including total white blood cell, lymphocyte percentage, and absolute lymphocyte count. During treatment, the peripheral blood of responders demonstrated dynamic losses followed by subsequent reappearance and expansion of CMV-specific CD4+ effector memory T cells. Based on these encouraging results, a new arm is enrolling subjects combining gB/pp65 eVLPs (at the same dose) formulated with adjuvant intramuscular $AS01_B$ and results will be presented.

CTIM-08. COMBINATION OF THE IMA950/POLY-ICLC MULTIPEPTIDE VACCINE WITH PEMBROLIZUMAB IN RELAPSING GLIOBLASTOMA PATIENTS

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The IMA950 peptide vaccine is composed of 9 HLA-A2-restricted peptides eluted from the surface of GBM samples and of two HLA class II-binding peptides[1]. It was tested in combination with poly-ICLC in patients with newly diagnosed GBM, demonstrating safety. The vaccine was able to elicit CD4 and CD8 T cell responses in the peripheral blood in the majority of patients, with however an overall low magnitude of T cell responses and suboptimal migration of elicited T cells to the brain, probably limiting clinical efficacy[2,3]. With the aim to improve homing of vaccine-specific T cell to the tumor, we are conducting a phase II clinical trial in patients with recurrent GBM testing the IMA950/poly-ICLC multipeptide vaccine with or without the anti-PD1 antibody pembrolizumab (NCT03665545). 24 patients will be included (12 patients in each arm) and pre- and post-vaccination tumor sample will be available, allowing assessing effect of the vaccine at the tumor site. The primary objective of this trial is safety of IMA950/poly-ICLC given together with pembrolizumab. Secondary objectives include (i) estimation of 6, 9 and 12-month progression-free survival (PFS), (ii) overall survival, (iii) analysis of patient quality of life and (iv) of the synergy/immunogenicity of IMA950/poly-ICLC and pembrolizumab. Immunomonitoring will include measure of vaccine-induced immune responses, IHC for immune cell markers, RNA/TCR sequencing and methylome analysis, to assess vaccine-induced T cell responses, immune modulation and potential signatures predictive of response. Thus far, 6 patients have been included (3 in each arm). Preliminary results show CD4 and CD8 T cell responses to the vaccine are detected in both groups in the peripheral blood. Analysis at the tumor site and comparison between arms will be performed once all patients have been included. 1. Dutoit, V. *et al. Brain* (2012); 2. Migliorini, D. *et al. Neuro Oncol* (2019); 3. Rampling, R. *et al. Clin Cancer Res*(2016)

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ERC1671 is an allogeneic/autologous therapeutic vaccine – composed of whole, inactivated tumor cells mixed with tumor- cell lysates. The hypothesized action of ERC1671 is to potentiate the patients' immune system against the tumor. Goals of this ongoing, phase 2 study are to determine the safety and effectiveness (overall survival) of ERC1671 in combination with GM-CSF and cyclophosphamide as an add-on treatment to bevacizumab at the time of GBM recurrence. To date 22 recurrent bevacizumab-naïve rGBM patients have been randomized to ERC1671/GM-CSF/Cyclophosphamide + Bevacizumab or Placebo + Bevacizumab. Median age is 56.5 (33–74), 7 patients (32%) are female, and average KPS is 82.3 (70–100). Of the 22, two discontinued before completing one cycle of therapy and two remain on blinded treatment. Currently 18 patients are unblinded due to further progression: 8 were on vaccine and 10 on placebo. Five of those on placebo crossed to vaccine at progression. All but one of the 18 are now deceased. Median overall survival of unblinded patients randomized to ERC1671 + Bevacizumab (n = 8) is 264.5 days from the start of study treatment, compared to 182 days for those randomized to placebo + Bevacizumab who did not cross over (n = 5). Median overall survival of unblinded patients on vaccine at randomization or crossover is 328 days after first study treatment (n = 13). While sparse, the data to date suggest pre-treatment and maximal CD4+T lymphocyte count in the peripheral blood correlate with OS more strongly in the ERC1671 group than in the placebo group. First clinical results for toxicity show no difference in the distribution of AEs between the Vaccine and Placebo groups, with no Gr4/Gr5 AEs in either group. This phase 2 randomized, double-blinded study is ongoing, with the addition of one more site.

CTIM-10. PHASE II STUDY OF PEMBROLIZUMAB PLUS SURVAXM FOR GLIOBLASTOMA AT FIRST RECURRENCE

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BACKGROUND: Pembrolizumab is a potent humanized immunoglobulin G4 monoclonal antibody with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 2 (PD-L2). Survivin is a 16.5 kDa intracellular protein that belongs to the inhibitor of apoptosis protein (IAP) family. It acts in concert with the mitotic spindle apparatus to regulate cell division and localizes to the spindle microtubule organizing center (MTOC) during the G2/M phase of cell cycle progression. Survivin has also been shown to modulate the function of a number of terminal effector cell death proteases (caspases) leading to an inhibition of apoptosis. METHODS: This is a Phase II study of two arms in patients with recurrent glioblastoma. Arm A is patients with first recurrence of glioblastoma who have failed prior chemotherapy and radiation but have not received any immunotherapy. Arm B is an exploratory arm of 10 patients who have failed prior anti-PD1 therapy. The ongoing study is a phase II clinical study with a 10 patient, toxicity run-in. All patients will receive the study drug combination consisting of SurVaxM and pembrolizumab with no randomization, stratification or dose escalation. RESULTS: So far ten patients have been enrolled on the study as safety run in. Primary endpoint is Progression free survival at 6 months. Safety and tolerability of Pembrolizumab and SurVaxM, Response rates of Pembrolizumab and SurVaxM determined using RANO criteria are secondary endpoints. Additional secondary endpoints include Overall