Title

ATIM-28. PHASE II TRIAL OF AV-GBM-1 (AUTOLOGOUS DENDRITIC CELLS LOADED WITH TUMOR ASSOCIATED ANTIGENS) AS ADJUNCTIVE THERAPY FOLLOWING SURGERY PLUS CONCURRENT CHEMORADIATION IN NEWLY DIAGNOSED GBM PATIENTS

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V dosing period was similar to Ad+V monotherapy with adverse reactions being dose-related and rapidly reversible upon discontinuation of V. And those adverse reactions during the follow on nivolumab dosing were tolerable and manageable and consistent with nivolumab labeling, with no synergistic toxicities, and drug-related deaths. In the first two cohorts (where data is available), combination therapy improved the biomarker "cytoindex" (ratio of circulating $CD8^+$ T cells to $FoxP3^+$ regulatory T cells). (In the Main study, cytoindex correlated with overall survival). Controlled IL-12 production using Ad+V with nivolumab is a rational combination with initial data consistent with immune-mediated anti-tumor effects with a favorable safety profile. Further phase 2 investigation of Ad+V plus a checkpoint inhibitor in rGBM is planned.

ATIM-26. INTERIM RESULTS OF THE EXTENSION PHASE OF 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 have initiated a phase I/IIa clinical trial for patients with recurrent GBM using gB/pp65 enveloped virus-like particles (eVLPs) formulated with GM-CSF and administered intradermally. In phase I, eligible patients were age 18–70 with Karnofsky Performance Status at least 70, normal end-organ function, on stable or decreasing corticosteroids of at most 4mg dexamethasone (or equivalent), with recurrent GBM following any standard initial therapy and any number of recurrences of any size. Patients were vaccinated monthly until tumor progression, with immune-monitoring performed 2 weeks after each vaccination and MRI exams every 6 weeks. The primary endpoint was safety/tolerability and secondarily to assess immunogenicity. Three vaccine doses (0.4μg, 2μg, and 10μg pp65) were evaluated with 6 patients in each cohort, and the DSMB identified no DLTs or safety concerns with any of the doses. The highest 10μg dose was chosen for the Phase IIa extension phase of the trial based on stable disease (3 months or longer) observed in 3/6 patients, which correlated with vaccine-induced IFN-γ-secreting T cell responses against CMV. Enrollment in phase IIa of the trial, which is designed to explore initial potential efficacy signals in an additional 10 patients that receive the optimal 10μg dose of vaccine, is expected in June 2019 and includes the additional requirements of unifocal, measurable enhancing tumor 1–3 cm across at first recurrence and no prior immunotherapy. Patients will be vaccinated monthly until clinical progression. Tumor responses and associated immunological biomarkers will be presented, and are expected to include initial data for all 10 patients.

ATIM-27. TUMOR MUTATIONAL BURDEN PREDICTS RESPONSE TO ONCOLYTIC POLIO/RHINOVIRUS RECOMBINANT (PVSRIPO) IN MALIGNANT GLIOMA PATIENTS: ASSESSMENT OF TRANSCRIPTIONAL AND IMMUNOLOGICAL CORRELATES

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BACKGROUND: The live attenuated oral poliovirus vaccine was modified to contain a heterologous internal ribosomal entry site stemming from human rhinovirus type 2, creating PVSRIPO. PVSRIPO recognizes CD155, an oncofetal cell adhesion molecule and tumor antigen widely expressed ectopically in malignancy. We have previously reported that deep sequencing of biopsy material obtained prior to PVSRIPO infusion confirmed that a very low mutational load is associated with longer survival. METHODS: Patient tumor material from both phase I and 2 clinical trials was collected pre PVSRIPO. When available, post-treatment tissue from longitudinal samples were also collected. Tissue was subjected to RNA sequencing, histological analysis, and flow cytometry analysis. RNAseq analyses were performed comparing pre- and post- treatment expression profiles and computational predictions of tumor immune composition deciphered changes after PVSRIPO therapy. Histology and flow cytometry quantitated myeloid, CD8/4/regulatory T cell densities, and other immune cell types after treatment and compared to baseline tissue similarly analyzed to detect changes. RESULTS: To date, analysis of phase 1 trial data has demonstrated a correlation between low TMB and increased markers of immunological gene expression profiles. This trend was not observed in TCGA samples that were almost exclusively primary GBM suggesting and interplay with prior therapy or evolution with recurrence. CONCLUSION: Our findings presented here suggest that response to PVSRIPO therapy, and possibly that of other modalities engaging innate antiviral signatures *in situ*, may be dependent upon prevailing tumor microenvironment composition/status at the time of treatment.

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Newly-diagnosed glioblastoma (GBM) patients have a limited survival (18–24 months). In the last decade immunotherapy has improved survival for patients with other malignancies, but not GBM. Herein we present the design and initial enrollment results for the AV-GBM-1 single-arm phase 2 trial. The study enrolls patients with primary GBM who have undergone craniotomy, have a tumor cell culture established, and complete satisfactory leukapheresis prior to planned concurrent chemotherapy and radiation. Patients are scheduled to receive up to 8 vaccine injections at weeks 1, 2, 3, 8, 12, 16, 20 and 24. Blood samples are collected just prior to each injection. The primary endpoint is overall survival from date of enrollment for intent-to-treat with AV-GBM-1. The study has fully enrolled 26 of planned 55 patients. The cell line success rate is 30/32, with 6 in progress; successful completion of leukapheresis is 28/29. Two patients have completed all 8 doses, two discontinued after dose 3 and dose 6 because of progressive disease; 15 are currently in treatment, and 6 are about to start treatment. There have been seven SAE, all for hospitalizations related to GBM. For the first 8 treated patients, plasma samples from baseline and weeks 2, 3, and 8 have been analyzed for immune markers by RayBiotech Life Inc. using quantitative multiplex ELISA array. Markers reflecting Th1, Th2, Th17 pathways and B-cells, natural killer cells and cytotoxic T-lymphocytes increased in 7/8 patients. Principal component analysis demonstrates correlative marker groupings with early dominance of Th1/Th17 (weeks 1 and 2) followed by Th2/immunoglobulins at week 8. These findings show that these patient-specific dendritic cell vaccines are inducing pro-inflammatory responses similar to what was observed in a previous trial in melanoma. The study is progressing efficiently. Full enrollment data may be available for presentation at the time of the annual meeting.

ATIM-29. IDENTIFYING IMMUNOLOGICAL BARRIERS TO IMMUNOTHERAPY IN PATIENTS WITH GLIOBLASTOMA MULTIFORME

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Recent successes in cancer immunotherapy have provided new avenues for the treatment of glioblastoma multiforme (GBM). Several immunotherapeutic approaches are now being utilized to treat patients with GBM including checkpoint inhibition, autologous/CAR-T cell therapy, and cancer vaccines. Preliminary data suggests that the majority of patients have sub-optimal clinical responses to these therapies. The impaired anti-tumor immune responses observed in these patients are likely a consequence of immune system dysfunction contributed to by a variety of factors that include diminished antigen presentation/detection, leukopenia, alterations in cytokine levels and cellular mediators. We have previously demonstrated that patients with GBM exhibit profound immune suppression resulting from both tumor and treatment related effects via a comprehensive quantitation of peripheral blood leukocytes by flow cytometry. We hypothesize that the depth and breadth of immunosuppression will significantly affect responses to immunotherapy. Prominent phenotypic abnormalities observed in GBM patients include elevated levels of $CD14^+HLA\text{-}DR^{lo/neg}$ monocytes and reduced absolute CD4 T cell counts. We will present data how these and other phenotypes may potentially influence responses to patients treated with dendritic cell vaccines. Our goal is to understand the role of these cells in the context of immunosuppression not only to facilitate the development of targeted immunotherapies to circumvent their effects, but also to potentially utilize them as biomarkers for understanding diverse responses to immunotherapies.