Title

ATIM-12. NEOADJUVANT ANTI-PD-1 IMMUNOTHERAPY PROMOTES INTRATUMORAL AND SYSTEMIC IMMUNE RESPONSES IN RECURRENT GLIOBLASTOMA: AN IVY CONSORTIUM TRIAL

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pheresis, 15 completed cycle 1. Median age 56 (27–69), median KPS 90; 11 were at 1st, 3 at 2nd and 1 at 3rd relapse. MGMT methylated in 6, unmethylated in 3, indeterminate/unknown in 6. IDH status wildtype in 10, mutated in 3, unknown in 2. No dose limiting toxicities (DLTs) observed. Complete radiographic response observed in 1 patient, partial response in 2, stable disease in 6, and progressive disease in 6. Repeated infusions of CMV-TC were associated with significant increase in circulating CMV+ CD8+ T-cells, but cytokine production (CD107a, TNFα, IFNγ, IL2) was suppressed (dose level 4 analysis ongoing). CONCLUSIONS: Adoptive infusion of CMV-TC after lymphodepleting therapy with ddTMZ was well tolerated with no DLTs; 1 x 10e8 confirmed as safe dose. Effector function in PB was suppressed. Correlative studies of CMV-specific T cell effector function in tumor microenvironment will be assessed in window-of-opportunity expansion cohort.

ATIM-12. NEOADJUVANT ANTI-PD-1 IMMUNOTHERAPY PROMOTES INTRATUMORAL AND SYSTEMIC IMMUNE RESPONSES IN RECURRENT GLIOBLASTOMA: AN IVY CONSORTIUM TRIAL

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Glioblastoma is the most common malignant brain tumor in adults and is associated with poor survival. It is often resistant to standard-of-care chemotherapy and radiation, necessitating the development of more effective treatments. The Ivy Foundation Early Phase Clinical Trials' Consortium conducted a randomized, multi-institution clinical trial to evaluate the immune response and survival following neoadjuvant and adjuvant therapy with pembrolizumab, a PD-1 monoclonal antibody, in thirty patients with recurrent, surgically resectable glioblastoma. Patients who received neoadjuvant pembrolizumab, with continued adjuvant therapy following surgery, had significantly extended overall survival compared to patients that received adjuvant, post-surgical PD-1 blockade alone (HR=0.33, p<0.008, log-rank test). Survival was directly associated with an elevated IFN-g gene expression signature in the tumor, but only in patients who received neoadjuvant PD-1 blockade (HR=0.15, p<0.02, Wald test). Focal induction of PD-L1 in the tumor microenvironment was observed in the neoadjuvant group and linked with the IFN-g gene expression signature and extended survival. Similarly, neoadjuvant pembrolizumab was associated with expanded T cell receptor clones, increased markers of activation in CD8+ T cells that expressed PD-1, and a decreasing monocytic population in the peripheral blood (p<0.03, two-sided t-test). These findings suggest that the neoadjuvant timing of PD-1 blockade enhances the local and systemic immune response, and may represent a more efficacious approach to the treatment of this uniformly lethal brain tumor.

ATIM-13. ASUNERCEPT PLUS RADIOTHERAPY IN RELAPSED GLIOBLASTOMA. UPDATE ON FIVE YEARS OVERALL SURVIVAL OF STUDY NCT01071837 AND DEVELOPMENT OF A POPULATION-PK - TUMOR GROWTH INHIBITION - SURVIVAL MODEL

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Asunercept (APG101) is an Fc-fusion protein consisting of the extracellular domain of human CD95 (APO-1/Fas) and the Fc domain of IgG1. Asunercept is in clinical development for glioblastoma (GB). Based on PK-data from study NCT01071837 a population pharmacokinetic (PopPK) - tumor growth inhibition (TGI) model was developed and extended to a survival model describing the effect of radiotherapy (RT) or RT + asunercept on the overall survival (OS) of GB-patients. The objective of the model was to identify the best descriptor (i.e. asunercept exposure, tumor size determined by MRT) for survival and to quantify the effect of CpG2 methylation in the CD95 ligand promoter on patient survival.

METHODS: Model development was performed using non-linear mixed effects modeling with NONMEM 7.3 in a stepwise procedure. Firstly, a PopPK–TGI model was developed. Several tumor growth models were tested (e.g. exponential, sequential exponential-linear). Secondly, a survival model was developed and linked to the PopPK-TGI model. RESULTS: For the PopPK-TGI model, data from 84 patients were available contributing to 314 tumor measurements. Glioblastoma growth was best described by an exponential growth model with an average doubling time of 90 days. Asunercept exposure showed a significant inhibitory effect on the tumor growth rate. Tumor size was identified to significantly influence survival. Incorporation of CpG2 CD95L promotor methylation further improved the model: the survival in asunercept-treated patients was prolonged with lower CpG2 methylation status. CONCLUSIONS: A PopPK-TGI-Survival model for asunercept and radiotherapy treated patients was developed. A clear inhibitory effect of asunercept exposure was observable on tumor growth resulting in an increased survival. A recent update on OS of study NCT01071837 revealed that 7% of Asunercept+RT treated 2nd-line GB patients were alive after 5 years compared to 0% in patients treated with RT alone.

ATIM-14. CMV gB/pp65 eVLPs FORMULATED WITH GM-CSF AS A THERAPEUTIC 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 highly immunogenic gB and pp65 antigens. We 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 are age 18–70 with KPS 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. The primary endpoint is safety/tolerability, and secondarily to assess immunogenicity. Additional requirements for phase IIa designed to explore efficacy include unifocal, measurable enhancing tumor 1–3 cm across at first recurrence and no prior immunotherapy. Subjects are vaccinated monthly until tumor progression, with immunomonitoring performed 2 weeks after each vaccination. Up to 3 different vaccine doses will be evaluated, with 6 subjects in each cohort; ten additional subjects will be enrolled once an optimal vaccine dose is identified. To date, 6 patients were accrued 4 men, 2 women, median age 55 (range 39–66) in the first dose cohort. Prior therapies include radiotherapy, temozolomide, and nivolumab. No DLTs were observed. Dose level 1 (0.4µg pp65 content, 200µg GMCSF) is completed and dose Level 2 (2µg pp65 content) is currently accruing. Preliminary analysis of the first 4 subjects demonstrates boosting of CMV-specific antibody titers and T cell responses in two patients, associated with increases (2-3-fold) in plasma levels of CCL3 and proinflammatory INF-g and TNF-a cytokines. These two subjects remain clinically stable without tumor progression after approximately 4 months on study. An expanded immunomonitoring data set will be presented along with associated clinical responses of the subjects.

ATIM-15. A PHASE 1 STUDY OF Ad-RTS-hIL-12 + VELEDIMEX IN ADULTS WITH RECURRENT GLIOBLASTOMA: DOSE DETERMINATION WITH UPDATED OVERALL SURVIVAL

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Ad-RTS-hIL-12 (Ad) is a novel gene therapy expressing IL-12 via the RheoSwitch Therapeutic System® gene switch under control of an oral activator ligand, veledimex (V). We previously reported on an open label Phase I trial describing biological activity of recombinant IL-12 with downstream IFN-γ and activation of the immune system. We provide an update on the intratumoral injections of Ad ($2x10^{11}$virus-particles) + V for patients with recurrent GBM (rGBM) in Group 1 (G1) (craniotomy, n=31) and initial results for Group 2 (G2) (stereotactic administration n=7). In G1, the V 20-mg cohort mOS increased to 12.7 months with mean follow-up of 12.9 months. 20-mg V in G1 showed fewer toxicities and higher V compliance (84%) compared with higher-doses of V (30 and 40-mg) with 75% and 67%, respectively. These