### Title

ATIM-20. A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED PHASE 2 STUDY OF THE ERC-1671 (GLIOVAC) VACCINE IN COMBINATION WITH BEVACIZUMAB (BEV) IN RECURRENT GBM PATIENTS: SAFETY LEAD-IN ANALYSIS




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of 6/14/2016, 14 patients have been treated (2 each at dose levels 1, 2, 4, 5 and 6 and 4 at dose level 3). One dose limiting toxicity was observed, a grade 4 seizure (dose level 3). Adverse events possibly related to study include: seizure (grade 4, n=1; grade 1, n=1); headache (grade 3, n=2; grade 2, n=4; grade 1, n=3); elevated ALT (grade 3, n=1; grade 1, n=2); fatigue (grade 2, n=2; grade 1, n=2); visual field cut (grade 2, n=1; grade 1, n=2); elevated AST (grade 2, n=1; grade 1, n=1); cognitive difficulties (grade 2, n=1; grade 1, n=4); stroke (grade 2, n=1; grade 1, n=1); nausea (grade 1, n=3), hemiparesis (grade 1, n=3); one each of grade 2 lymphopenia, generalized muscle weakness, dysphasia, hemineglect, paresthesia, and venous thromboembolic event; and one each of grade 1 anemia, thrombocytopenia, elevated alkaline phosphatase, blurred vision, vomiting, and gait difficulties. Ten patients remain alive with one patient disease-free more than 10 months after infusion. CONCLUSION: Infusion of D2C7-IT via CED is safe thus far and encouraging efficacy results are observed. Enrollment is ongoing.

**ATIM-19. CATEGORIZING IMMUNE RESPONDERS WITH FUSION METRICS AND SIMULATION FOR ASSOCIATION TO SURVIVAL AND PROGRESSION FREE SURVIVAL WITH IMMUNE RESPONSE IN HLA-A2+ PATIENTS WITH GBM FROM A PHASE 2 TRIAL OF DENDRITIC CELL (DC) IMMUNOTHERAPY (ICT-107)**

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BACKGROUND: Detailed confirmatory testing and analysis verifies and strengthens the association between clinical outcomes and immune response of HLA-A2+ patients enrolled in a randomized phase 2 trial of ICT-107. METHODS: 77 HLA-A2+ patients, randomized 2:1, received ICT-107 (autologous DCs incubated with 6 synthetic peptide CTL epitopes targeting GBM tumor/stem cell-associated antigens, including the four HLA-A2-restricted antigens HER-2, TRP-2, gp100, and IL-13Rα2) or matching control (un-incubated DC). Multimer testing was performed on a subset of these patients. The pioneering analysis heuristic of fusion metrics used in conjunction with Monte Carlo simulation was used to identify multimer immune responders. P-values between dependent variables and multiple overall survival (OS) or progression-free survival (PFS) metrics was performed using log-rank test and Fisher's exact test. RESULTS: HLA-A2+ patients consistently continued to show evidence of immune response being associated with both OS and PFS. Multimer immune responders independently confirmed the ELISpot immune responder associations between assignment group (p=0.0308), and initial OS and PFS (p=0.0043 and 0.0352, respectively). Combining ELISpot and multimer responders strengthened or maintained associations with all OS and PFS metrics. Notable significant associations were determined when data was stratified by treatment group in both treatment and placebo subgroups, leading to speculation of the possible positive effects of DCs alone. This finding supports changing the placebo in the Phase III study from dendritic cells to PBMCs. CONCLUSIONS: The robust associations identified between OS and PFS with immunologic response, explored using both multimer and ELISpot analysis to determine immune response with fusion metrics in a Monte Carlo setting, provide support for the efficacy of ICT-107 to induce peptide-specific T cell responses in HLA-A2+ patients.

**ATIM-20. A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED PHASE 2 STUDY OF THE ERC-1671 (GLIOVAC) VACCINE IN COMBINATION WITH BEVACIZUMAB (BEV) IN RECURRENT GBM PATIENTS: SAFETY LEAD-IN ANALYSIS**

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BACKGROUND: Recurrence of malignant gliomas following surgery, radiation therapy and adjuvant chemotherapy is nearly universal. The only approved second-line treatment for malignant gliomas is Bevacizumab (Avastin), with estimated 6-month progression-free survival rates of less than 40%. Ultimately, all the GBM patients relapse on Bevacizumab, and no other effective therapies are available. ERC-1671 aims at stimulating the patients' immune system by including patient's glioblastoma tumor as lysates and cells as well as heterologous component generated from three different GBM donors. The NCT01903330 study opened in 2014, and was mandated by the FDA to start with a single –institution, safety lead-in phase before extending to multiple centers. METHODS: Eligible patients were over 18 years of age, had histologically confirmed WHO grade IV malignant glioma and have failed the treatment with radiation and temozolomide. Primary end points are toxicity and 6-month progression-free survival (PFS) while secondary endpoints are safety and overall survival (OS). RESULTS: Data reported as May 1st, 2016 - we have enrolled eight patients - which completed the safety lead-in analysis. Median age was 57, with 2/8 female patients. The average KPS was 80 (70–100). Four patients have stable disease, and their treatment group is not known to the investigator. Four patients had disease progression (at which point the protocol allows for un-blinding), two in the active treatment group and two in the control (BEV) group. No grade 4 or 5 AEs occurred. The grade 3 AEs were intracranial hemorrhage (in the control group), muscle weakness/myalgia (in the control group) and headaches (all three group). The most common AE was headache. CONCLUSION: Based on this safety report, we have now amended the study to allow multi-site enrollment. Updated results will be presented at the SNO meeting.

**ATIM-21. IMA950 PEPTIDE-BASED VACCINE ADJUVANTED WITH POLY-ICLC IN COMBINATION WITH STANDARD THERAPY IN NEWLY DIAGNOSED HLA-A2 GLIOBLASTOMA PATIENTS: PRELIMINARY RESULTS**

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Phase I/II trial: HLA-A2 positive newly diagnosed GBM patients received after surgery, standard concurrent chemoradiation with temozolomide. In addition patients underwent 6 (before protocol amendment) or 4 (after protocol amendment) vaccinations of IMA-950 with poly ICLC (TLR3 agonist) once a week starting one week after the end of radiation, then 5 vaccinations once a month alternately with the 6 cycles of temozolomide. Primary endpoint was safety, secondary were OS, PFS at 6, 9 months, and immunological endpoints. 19 patients have been enrolled. The first 6 patients received the vaccine intradermally and the adjuvant intramuscularly (IM) in close vicinity and the site varied to stimulate the major draining lymph nodes. The preliminary analysis of vaccine-induced T cell responses didn't show any induction of peptide-specific CD4 or CD8 T cells, leading to design a novel vaccination schedule/formulation. An amendment in the protocol incorporated the following changes: mixing vaccine/adjuvant before injection at one single site (thigh), decreasing the number of vaccinations during the induction phase, testing two different injection routes for the remaining 13 patients (subcutaneously or IM). Clinically, IMA-950 was well tolerated, the most common side effect was local inflammatory reaction at the injection site with mild fever. Some patients experienced cerebral edema, manageable with steroids. Among the 6 first patients, 2 showed disease progression, and median OS was 17.5 months (11–21). Patients under the amended protocol are still under therapy for 3 of them and 5 others finished the study protocol and are being followed without tumor recurrence. Analysis of vaccine-induced T cell responses in two of the 13 amended patients showed induction of both peptide-specific CD4 and CD8 T cells, suggesting those changes might lead to better immunization. IMA-950 is safe, preliminary mOS seems to be improved. Objective immune responses in two patients were observed.

**ATIM-22. PLACEBO CONTROLLED DOUBLE BLIND PHASE IIB/III TRIAL OF AUTOLOGOUS FORMALIN-FIXED TUMOR VACCINE (AFTV-GBM) FOR NEWLY DIAGNOSED GLIOBLASTOMA**

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There has been a growing interest in therapeutic modalities based on tumor-specific immune reactions for glioblastoma(GBM). Autologous formalin-fixed tumor vaccine(AFTV) for GBM is an emerging innovative treatment approach, which aims at stimulating patient's own immune system. Based on retrospectively analyzed clinical results of AFTV phase I/II trials, we are conducting double-blind phase IIb/III clinical trial. We have finished two phase I/II trials of AFTV in ACNU era and TMZ era. Newly diagnosed GBM with KPS>60, 16-75yo, more than 80% removal were enrolled for the analysis. Three courses of AFTV were administered after initial treatment radiation without chemotherapy in ACNU era (UMIN0002) and radiation with TMZ in TMZ era as first line therapy(UMIN1426). Median overall survival (mOS) and progression free survival (mPFS) were 19.8 and 7.6 months respectively in UMIN0002. Second AFTV trial resulted in 22,2 and 8,2 months in UMIN1426. There were no significant adverse events of more than grade2. The results of these trials demonstrate the feasibility of AFTV as concomitant treatment of 1stline therapy. We are ongoing multicenter double-blind prospective randomized phase II/III trial. The study is designed as prospective placebo-control double blind trial. 60 pts were enrolled for phase IIb part. Three course of AFTV were administered before, end and one month after initial treatment of chemo and radiation therapy. OS as primary endpoint and PFS, response rate and QOL are observing. We introduce the rationale and study design of this clinical trial.

**ATIM-23. PHASE 1 DOSE ESCALATION STUDY OF CONTROLLED INTRATUMORAL VIRAL DELIVERY OF Ad-RTS-hIL-12 + ORAL VELEDIMEX IN SUBJECTS WITH RECURRENT OR PROGRESSIVE HIGH-GRADE GLIOMA**

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BACKGROUND: Ad-RTS-hIL-12 is a novel gene therapy candidate expressing IL-12 under the control of an orally administered activator