ATIM-15. A PHASE I TRIAL OF HYPOFRACTIONATED STEREOTACTIC IRRADIATION (HFSRT) WITH PEMBROLIZUMAB AND BEVACIZUMAB IN patients with recurrent high grade gliomas
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BACKGROUND: High grade gliomas carry a grim prognosis despite current therapies. Expression of PD-1 and PD-L1 is found in the microenvironment of most high grade gliomas. There is strong preclinical evidence for the combination of anti PD-1/PD-L1 blockade with radiotherapy and anti-angiogenic agents. This study evaluates the combination of pembrolizumab, an anti-PD-1 monoclonal antibody, with hypofractionated stereotactic irradiation (HFSRT) and bevacizumab. METHODS: This phase I study (3+3 design) explores the safety, tolerability, recommended phase II dose (RP2D), and antitumor activity of pembrolizumab administered concurrently with HFSRT and bevacizumab (NCT02313272). Adult patients with recurrent glioblastoma (GBM) or anaplastic astrocytoma (maximum diameter of target lesion ≤ 3.5 cm) are eligible. Eligible patients receive HFSRT to the recurrent tumor (30 Gy delivered in 5 fractions) combined with pembrolizumab (100 mg/kg, intravenously) and bevacizumab (100 mg or 200 mg intravenously based on dose level, Q3W). Two dose levels of pembrolizumab (100 mg and 200 mg Q3W) are explored. After determination of RP2D, an additional 20 patients will be enrolled in an expansion cohort (50 mg or 100 mg, every 2 weeks) is well tolerated. No dose limiting toxicity or treatment-related neurologic adverse event has been observed. Six out of nine patients have achieved objective response (complete response + partial response). CONCLUSION: Preliminary data demonstrate an acceptable toxicity profile and encouraging anti-tumor activity. Updated safety and efficacy data will be presented.

ATIM-17. INVESTIGATION OF ANTITUMOR CELLULAR IMMUNE RESPONSE ELICITED BY TOCA 511 & TOCA FC THERAPY IN A RECURRENT HGG PHASE I TRIAL
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A dose-escalation clinical study (NCT01470794) using a retroviral replicating vector (RRV), Toca 511, in combination with oral Toca FC (extended-release 5-fluorocytosine [5-FC]) is ongoing to evaluate safety and preliminary efficacy of this investigational therapy in patients with recurrent HGG. Toca 511 (vocimagene amiretrorepvec) encodes a yeast-derived, codon-optimized, heat-stabilized cytosine deaminase (CD) that converts 5-FC to the anti-cancer drug 5-FU in infected tumors. This virus replicates preferentially in malignant tissue and may have wide application in cancer therapies. When Toca FC is administered, the infected cells are killed by the 5-FU metabolized from 5-FC by the cytosine deaminase protein. In animal tumor models, as infected cancer cells are killed, the diffusible 5-FU also kills neighboring susceptible cells, including myeloid immune suppressor cells that the cancer has attracted to set up an immune-suppressed tumor microenvironment. The killed cancer cells release molecules, such as DAMPs, PAMPs and TLRs that activate antigen presenting cells against released tumor-specific antigens. These tumor antigens are presented to the otherwise intact immune system in the absence of local tumor mass, leading to a robust antitumor immune response that targets tumor specific antigens. In the clinical study presented here, Toca 511 is injected into resection cavity walls at time of tumor resection, and followed with multiple courses of Toca FC, Temporal lobe tumors in PBMC populations during treatment were measured. This included: subtyping of effector, memory, Treg, and myeloid derived suppressor cell panels by flow cytometry; and specific antitumor activity by assays for tumor reactive peripheral blood monocyte (PBMC). Tumor and blood exome sequencing was performed to assess immunogenic potential of the tumor before and after treatment of tumors with Toca FC. A multivariate analysis using immune data and clinical factors will be presented. Clinical data are consistent with the induction of anti-tumor immune responses after Toca FC administration.

ATIM-16. NIVOLUMAB COMBINED WITH RADIOTHERAPY WITH OR WITHOUT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED Glioblastoma: RESULTS FROM PHASE 1 SAFETY COHORTS IN CHECKMATE 143
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BACKGROUND: Patients with glioblastoma have a poor prognosis, with 5-year survival rates <5%. Nivolumab is an IgG4 monoclonal antibody inhibitor of programmed death 1 (PD-1) receptor with demonstrated efficacy in various tumor types. In phase 1 cohorts 1c and 1d of Checkmate 143 (NCT02313272), the safety and tolerability of nivolumab with radiotherapy ± temozolomide was evaluated in patients with newly diagnosed glioblastoma. METHODS: Following surgery, patients in cohort 1c received nivolumab ± temozolomide was evaluated in patients with newly diagnosed glioblastoma. RESULTS: As of March 23, 2016, treatment has been well tolerated. Treatment discontinuation in cohorts 1c (26%) and 1d (35%) was due primarily to radiographic progression (1c, 10%; 1d, 35%) and withdrawal consent (1c, 10%). Most frequent treatment-related adverse events (AEs) included fatigue (1c, 1d: 26%, 23%), headache (23%, 8%), and increased AST (23%, 0%), Treatment-related serious AEs reported in ≥2 patients were pneumonia (6%, 0%), pyrexia (6%, 0%) and tumor flare (3%, 8%), characterizing either disease progression or pseudoprogression. AEs leading to discontinuation were increased amino transferases (n=2 [1c]). No treatment-related deaths have been reported. CONCLUSION: CheckMate 143 demonstrated the feasibility and well toleratedness of the combination of nivolumab with radiotherapy ± temozolomide and will be evaluated in the following phase Ib/IIa trials: CheckMate 146 (radiotherapy ± temozolomide) and CheckMate 912 (radiotherapy ± pembrolizumab), to evaluate the safety and antitumor activity of nivolumab in newly diagnosed glioblastoma.
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: sickness grade 1 (n=11); 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=2); elevated AST (grade 2, n=1; grade 1, n=1); peripheral neuropathy grade 1 (n=1); peripheral neuropathy grade 1 (n=1); 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 gast dilatations. Ten patients reported patient disease-free more than 10 months after infusion. CONCLUSION: Infusion of DC27-FIT 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 AND 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 responses 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-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 Fischer's exact test. RESULTS: HLA-A2+ patients consistently showed 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 MonteSpot 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 II trial. 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-BLIND, PLACEBO-CONTROLLED PHASE 2 STUDY OF THE ERC-1671 (GLIOVAC) TUMOR 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 a vaccine (autologous DCs incubated with 6 synthetic peptide CTL epitopes targeting GBM-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 Fischer’s exact test. RESULTS: ERC-1671 patients consistently showed 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 MonteSpot 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 II trial. 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-21. IMA950 PEPTIDE-BASED VACCINE ADJUVANTED WITH POLY-I:CLC IN COMBINATION WITH STANDARD THERAPY IN NEWLY DIAGNOSED HLA-A2 GliOBLASTOMA PATIENTS: PRELIMINARY RESULTS

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Phase III trial: HLA-A2 positive newly diagnosed GBM patients received after surgery, standard concurrent chemoradiation with temozolomide. Phase I trial: before protocol amendment or 4 (after protocol amendment) vaccinations of IMA-950 with poly I:CLC (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 5 patients received the vaccine intradermally and the adjuvant intra muscularly (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 follow 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 first 6 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 III/II 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 previous phase III/II trials, we are conducting a double-blind phase III/II clinical trial. We have finished two phase III trials of AFTV in ACNU era and TMZ era. Newly diagnosed GBM with KPS>60, and 6 and 4 at dose level 3). One dose limiting toxicity was observed, a grade 2 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-23. PHASE 1 DOSE ESCALATION STUDY OF CONTROLLED INTRATUMORAL VIRAL DELIVERY OF Ad-RTS-hIL-12 PLUS 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