

progressive physical and mental debilitation culminating in death. 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 (over-all 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 16 recurrent bevacizumab-naïve GBM patients have been randomized to ERC1671/GM-CSF/Cyclophosphamide + Bevacizumab or Placebo + Bevacizumab. Median age is 56.5 (39–74), 5 patients (31%) are female, and average KPS is 83 (70–100). Thirteen patients are deceased and were unblinded at the time of further progression: 5 received vaccine, 7 received placebo, and 1 is non-evaluable due to discontinuation before completing 1 cycle. Median overall survival of the deceased patients treated with ERC1671 + Bevacizumab was 328 days (10.9 months), compared to 245 days (8.2 months) for patients treated with Placebo + Bevacizumab. 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. The phase 2 randomized, double-blinded study is ongoing with the addition of 2 subsites.

ATIM-43. PLASMA EXTRACELLULAR VESICLE MIRNA SIGNATURES IN GBM PATIENTS RECEIVING AN EXPERIMENTAL IMMUNOTHERAPY

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Patients with glioblastoma (GBM) have a median survival of 15 months despite aggressive treatment. Immunotherapies such as dendritic cell (DC) vaccines have modest clinical efficacy in small clinical trials. Treatment-related pseudo-progression confounds outcome assessment by MRI, particularly in patients receiving immunotherapy. Thus, there is a need for additional non-invasive methods to monitor treatment response. Extracellular vesicles (EVs), especially plasma exosomes, contain tumor-specific microRNA (miRNA) cargo that could serve as a liquid biopsy to distinguish true progression from treatment-related pseudo-progression. Plasma exosomes were isolated by serial density gradient ultracentrifugation from 20 newly diagnosed GBM patients enrolled in a clinical trial of allogeneic tumor lysate-pulsed autologous DC vaccination. Short non-coding RNA sequencing and bioinformatics analysis was performed for each patient at three time points (TP): pre-vaccine (TP1), post-initial vaccine (TP2), and at end of treatment (TP3). miRNA expression analysis revealed a total of 14 upregulated and 12 downregulated miRNAs across time points (p -value < 0.05, \log_2FC > 1), few of which have been previously reported to be differentially expressed in GBM. Interestingly, patients' miRNA profile expression differed more at the beginning of treatment (e.g. TP1-vs-TP2) and at subsequent time points (e.g. TP2-vs-TP3). Ingenuity Pathway Analysis is in progress to identify pathways associated with immunotherapy treatment response in malignant gliomas. In conclusion, miRNA sequencing from GBM patients' plasma exosomes enrolled in our DC clinical trial shows marked differential miRNA expression between time points. These results suggest that as patients progress through treatment, consistent differences in plasma exosomal miRNA expression profile can be identified that could be utilized as predictors of treatment response. Thus, plasma EVs may serve as a robust platform to monitor treatment outcome.

ATIM-44. A PHASE I FIRST-IN-HUMAN TRIAL OF TWO ADENOVIRAL VECTORS EXPRESSING HSV1-TK AND FLT3L FOR TREATING NEWLY DIAGNOSED RESECTABLE MALIGNANT GLIOMA: THERAPEUTIC REPROGRAMMING OF THE BRAIN IMMUNE SYSTEM

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This is an interim report on a first in human Phase I dose escalation trial of the combination of two adenoviral vectors expressing HSV1-TK or Flt3L

for the treatment of newly diagnosed, resectable malignant gliomas. Lack of dendritic cells from the brain precludes anti-glioma immune responses. We combined tumor cytotoxicity (Ad-HSV1TK) with recruitment of dendritic cells to gliomas (Ad-Flt3L) to induce anti-glioma immunity. In experimental models this treatment induces powerful cytotoxic CD8 and CD4 T-dependent anti-glioma immunity, immunological memory, and the capacity to recognize neo-antigens. The trial was approved through a FDA-IND, and all institutional ctees. Treatment was administered intraoperatively following complete glioma resection in newly diagnosed tumors. The trial consisted of vector dose escalation, starting at 1×10^9 v.p., and increasing to 1×10^{11} v.p. of each vector, through 6 cohorts of 3 patients each. Two cycles of 14 days of valacyclovir were administered to activate HSV1-TK cytotoxicity. Cycle 1 starts on Day 1–3 post surgery for 14 days, and Cycle 2 on Week 8–12. Standard radiation, i.e., 60 Gy in 2 Gy fractions over 6 weeks, with concurrent temozolomide, was followed by cyclic temozolomide. Examination of tumor samples at primary resection and first recurrence show an increase in the infiltration of inflammatory cells. The experimental treatment was well tolerated. An MTD was not reached. There were approx. 248 AEs, and 26 SAEs; these were not linked to treatment. As secondary outcome, median survival of contemporary controls was 604 days, and median survival of trial patients was 742 days. Our results show for the first time that reprogramming of the host's brain immune system to recognize gliomas reveals a new approach for the treatment of highly malignant brain tumors. Clinical trial information: NCT01811992.

ATIM-45. LONG TERM FOLLOW-UP OF A PHASE I/II STUDY TESTING THE TOXICITIES AND EFFICACY OF PEMBROLIZUMAB IN COMBINATION WITH MRI-GUIDED LASER INTERSTITIAL THERMAL THERAPY (LITT) IN RECURRENT MALIGNANT GLIOMAS

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BACKGROUND: LITT was recently demonstrated to induce temporary blood-brain barrier disruption, possibly allowing bilateral trafficking of tumor neoantigens and immune cells to induce glioma-specific immune activation - a phenomenon akin to in situ tumor vaccination. We hypothesize that combining LITT with immune checkpoint inhibition will create a synergistic therapy for recurrent GBM. **METHODS:** The phase 1 study is a standard 3x3 design with a maximum of 18 patients with bevacizumab-naïve recurrent WHO grade 3–4 glioma. The primary endpoint is safety and toxicity of LITT plus pembrolizumab at 100, 150, or 200mg IV q3weeks. Phase 2 includes 40 patients with bevacizumab-naïve recurrent GBM, equally randomized to either pembrolizumab alone or LITT plus pembrolizumab, with progression-free survival as the primary endpoint. Serial immunophenotyping will be performed to evaluate potential positive synergy between LITT and pembrolizumab. **RESULTS:** Phase 1 accrual was completed with 9 patients (3 at each pembrolizumab dose level). Two had recurrent anaplastic astrocytoma and 7 recurrent GBM. There was no dose-limiting toxicity with pembrolizumab 200mg IV q3weeks. The median number of doses given per patient was 9 (range 2 to 47). Severe adverse events possibly related to the study treatment included a grade 3 rash and diarrhea in 1 patient (11%) and grade 3 pneumonitis and hypotension in another patient (11%). No grade 3/4 intracranial edema deemed related to study treatment was observed. To date, four (44%) of these patients are still alive without tumor progression. Two (22%) GBM patients have not progressed for 29 and 33 months, respectively. Two (22%) anaplastic astrocytoma patient have not progressed for 23 and 24 months, respectively. **CONCLUSIONS:** LITT plus pembrolizumab 200mg IV q3weeks is well tolerated in patients with recurrent high-grade glioma. Prolonged stable diseases were observed in almost half of patients treated. Phase 2 study is ongoing and will be updated.

ATIM-46. A MULTICENTER, PHASE I, TRIAL OF RADIATION, TEMOZOLOMIDE AND RRx-001 FOLLOWED BY MAINTENANCE TEMOZOLOMIDE WITH OR WITHOUT RRx-001 IN NEWLY DIAGNOSED GLIOBLASTOMA PATIENTS

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BACKGROUND: RRx-001 is an aerospace-derived radiochemosensitizer with minimal toxicity. The purpose of this trial was to establish the safety of RRx-001 plus radiotherapy and temozolomide and to look for signals of enhanced anti-tumor activity in patients with newly diagnosed glioblastoma. **METHODS:** In this non-randomized trial called G-FORCE-1 (NCT02871843), 18 newly diagnosed, histologically verified