Title

ATIM-42. DOUBLE-BLINDED, PLACEBO CONTROLLED PHASE 2 STUDY OF ERC1671 IN RECURRENT GLIOBLASTOMA: OS CORRELATIONS WITH INITIAL AND MAXIMUM CD4+T LYMPHOCYTE COUNT IN THE PERIPHERAL BLOOD

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formed *IDH*-mutant GBMs. Safety-lead-in results will be presented. METHODS: This is a phase II, open-label, single-arm, multicenter study of Avelumab with HFRT in adults with transformed *IDH*-mutant GBM who previously received RT and TMZ and/or PCV. All pts received Avelumab 10 mg/kg IV followed at Day 8 by HFRT (25 Gy in 5 daily 5-Gy fractions) and then Avelumab 10 mg/kg IV every 2 weeks. A 3 + 3 design was used for a 6-patient safety-lead-in cohort. Adverse events were recorded according to CTCAE. RESULTS: Six pts (F=4, M=2) with a median age= 45.5 yrs (range 31.5–54.4 yrs) were enrolled in the safety-lead-in cohort. No DLT was observed. Grade ≥ 3 AEs included increased cerebral edema (3 pts), hyponatremia (1 pt) and worsening hemiparesis (3 pts). Grade ≤ 2 AEs included nausea, hypothyroidism, lymphopenia, thrombocytopenia, transaminase elevation, and fever/chills. Median follow-up time was 8.9 mo. Best treatment response was SD in 1 patient. At time of last follow-up all pts have discontinued treatment for PD. Median PFS was 4.2 mo (range 1.4–5.7). Median OS was 10.1 (range 6.8–21+) mo. 4 pts (67%) died, 2 pts remain alive in follow-up at 6.9 and 21.6 months after treatment initiation. The study was closed after the safety lead-in completed enrollment due to slow accrual. CONCLUSIONS: Avelumab combined with HFRT was tolerable without dose-limiting toxicity in this safety-lead-in cohort of adult patients with transformed *IDH*-mutant GBM. Further studies are necessary to determine efficacy of this treatment regimen.

ATIM-38. GLITIPNI: A PHASE 1B CLINICAL TRIAL COMBINING SURGICAL RESECTION WITH DIRECT INTRACEREBRAL INJECTION OF IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH RECURRENT GLIOBLASTOMA

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INTRODUCTION: Intravenous (iv) administration of PD-1 blocking mAb is largely ineffective for the treatment of recurrent glioblastoma (rGB). Combination of iv-ipilimumab (IPI) plus nivolumab (NIVO) is associated with a high incidence of irAE. Intracerebral (ic) administration of immune-checkpoint inhibiting mAb following the resection of rGB could be a more effective and safer alternative to iv-dosing. METHODS: Patients underwent maximal safe resection of their rGB followed by ic-injection of 10mg IPI (cohort-1) or 5mg IPI plus 10mg NIVO (cohort-2) in the wall of the resection cavity. In both cohorts 10mg nivolumab was administered iv for a max of 6 doses, starting 1 day pre-operatively. RESULTS: 21 pts were included (3 in C-1, 18 in C-2; 8F/13M; median age 56y [range 38–72]; 17 de novo GB, 4 secGB). All patients underwent maximal safe surgical resection followed by ic-injection of IPI and NIVO as planned. Median number of iv-administrations of NIVO was 5 (range 1–8). Treatment was generally well tolerated. Postoperatively, 2 patients experienced a G3 symptomatic increase in perilesional cerebral edema with neurological deterioration, reversible upon steroid treatment. One patient had worsening neurological symptoms related to an inflammatory intracerebral cyst at the resection site, requiring surgical decompression 4 months post-study treatment. Most frequent AEs were fatigue (2pts G3, 8pts G2), postoperative fever (11pts G1) and headache (3pts G2); 1pt developed G3 pneumonitis. No other immune-related AEs or treatment-related deaths occurred. After median follow-up of 60 weeks, median PFS is 14.4 weeks (95% CI 11.2–17.6); 11/21 patients are alive, and 1- and 2y-OS% are respectively 46% (95% CI 19- 73%), and15% (95% CI 0–42%). CONCLUSION: This is the first study demonstrating the safety and activity of combined surgical resection of rGB with local intracerebral administration of immune checkpoint-inhibiting mAb. Survival compares favorably to historical controls justifying further investigation of this experimental therapy.

ATIM-39. PHASE 2 OPEN-LABELED STUDY OF ADJUVANT TEMOZOLOMIDE PLUS TUMOR TREATING FIELDS PLUS PEMBROLIZUMAB IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA (2-THE-TOP)

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BACKGROUND/OBJECTIVE: Tumor treating Fields (TTFields) plus maintenance temozolomide is an approved standard treatment for newly diagnosed Glioblastoma (GBM). TTFields are alternating electric fields of low intensity and intermediate frequency delivered non-invasively via transducer arrays to tumor region. Immune checkpoints have not been studied widely in newly diagnosed GBM patients. TTFields combined with temozolomide elicit anti-mitotic effects on proliferative cancer cells and augment recruitment of immune effector cells specific for glioma cells to the tumor microenvironment where pembrolizumab further potentiates the immune reaction to achieve a synergistic therapeutic effect. This study [NCT03405792] will determine if adding pembrolizumab to TTFields and maintenance temozolomide (triple combination) increases progression-free survival (PFS) in patients with newly diagnosed GBM versus historical control (EF-14). METHODS: This study will enroll patients (N=24) with pathologic diagnosis of newly diagnosed GBM WHO grade 4, ≥ 18 years after maximal surgery or biopsy followed by radiation therapy with adjuvant temozolomide (Stupp protocol). The primary endpoint is increases in PFS compared to historical control data (EF-14). Secondary endpoints include: toxicity and tolerability of the triple combination; overall survival and response rates versus historical data; augmentation of TTFields-initiated glioma-specific immune reaction by pembrolizumab. Exploratory endpoints include: metabolomics signature of immune activation by TTFields and TTFields plus pembrolizumab in serum and urine, and correlation of mutation burden in primary tumor samples with response to pembrolizumab plus TTFields. We assumed an accrual period of 12 months, an accrual rate of 2 patients per month, an additional 18 months of follow-up, and proportional hazards. Per shape parameter estimate of k=0.88 with empirical 95% confidence interval (0.82, 0.95) obtained via simulation of historical control data, a sample size of 24 patients should detect an improvement in PFS of 6 to 8 months with 80% power and a 1-sided significance level of 0.05 (Wu and Xiong, 2014).

ATIM-40. CIRCULATING MYELOID-DERIVED SUPPRESSOR CELLS PREDICT FAVORABLE RESPONSE TO IMMUNE CHECKPOINT THERAPY IN A RANDOMIZED TRIAL OF NIVOLUMAB AND BEVACIZUMAB IN RECURRENT GBM

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Glioblastoma (GBM) creates an immunosuppressive environment that presents a challenge to efficacy of immunotherapeutic approaches. Results from the CheckMate-143 trial demonstrated responses in 8% of patients with nivolumab, underscoring the need for further insight into the mechanisms and markers of immune suppression and response. Given a limited set of biomarkers predictive of immunotherapy response in GBM, we explored the changes in immune cell populations in nivolumab and bevacizumab-treated GBM patients pre and post-treatment in order to help predict response. In these studies, we utilized traditional and newly developed approaches, including mass cytometry time-of-flight (CyTOF), single-cell RNA sequencing, and 10X Genomics simultaneous cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq). We analyzed patients' samples in a randomized, phase 2 study of nivolumab and bevacizumab at GBM first recurrence (NCT03452579). Nine patients were identified as responders or non-responders at 8 weeks after therapy initiation. Utilizing peripheral blood samples, we observed a 6.4-fold decrease in immunosuppressive myeloid-derived suppressor cells (MDSCs) between baseline and first imaging follow-up in responders compared to non-responders, with a 4.9-fold decrease in the granulocytic MDSC (G-MDSC) subtype in responders over non-responders. While no significant changes in overall T-cell numbers were noted, expression of PD-1 on CD4+ T cells was significantly elevated at baseline and follow-up in responders as compared to non-responders – signatures which were confirmed by CyTOF. Given these immunophenotypic changes, preliminary results of a detailed investigation of this cohort by CITE-seq indicate that responders had increased IL7R-positive T cells post-treatment, which was not observed in non-responders. These results are currently being validated in an additional 40 patients that have been enrolled. Altogether, differences in immunophenotypes that were specific to responders and non-responders were observed, and characterization of these immune populations may be helpful in identifying GBM patients likely to benefit from immunotherapy.

ATIM-42. DOUBLE-BLINDED, PLACEBO CONTROLLED PHASE 2 STUDY OF ERC1671 IN RECURRENT GLIOBLASTOMA: OS CORRELATIONS WITH INITIAL AND MAXIMUM CD4+T LYMPHOCYTE COUNT IN THE PERIPHERAL BLOOD

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Standard therapy for recurrent GBM is bevacizumab, a monoclonal VEGF inhibitor that targets tumor vascularization. The response to bevacizumab is transient and short-lived (4–6 months) after which patients typically develop

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 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 pseudoprogression 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, |logFC| >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 cttees. Treatment was administered intraoperatively following complete glioma resection in newly diagnosed tumors. The trial consisted of vector dose escalation, starting at 1x10^9 v.p., and increasing to 1x10^11 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 pemprolizumab 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