Title

ATIM-21. INTRAVENOUS DELIVERY OF TOCA 511 IN PATIENTS WITH HIGH GRADE GLIOMA RESULTS IN QUANTIFIABLE EXPRESSION OF CYTOSINE DEAMINASE IN TUMOR TISSUE

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limiting toxicity with pembrolizumab 200mg IV q3weeks. The median number of doses given per patient was 5 (range 2 to 12). 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. Best response was stable disease. One (11%), 2 (22%), and 1 (11%) GBM patients have not progressed for 20.7, 8, and 4 months, respectively. One (11%) anaplastic astrocytoma patient has not progressed for 12 months. **CONCLUSIONS:** LITT plus pemprolizumab 200mg IV q3weeks is generally well tolerated in patients with recurrent high-grade glioma. Prolonged PFS was observed in several patients. Updated study data will be presented. The study should proceed to the planned phase 2.

ATIM-18. A PHASE I TRIAL OF HYPOFRACTIONATED STEREOTACTIC IRRADIATION (HFSRT) WITH PEMBROLIZUMAB AND BEVACIZUMAB IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMA (NCT02313272)

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BACKGROUND: There is strong pre-clinical evidence for the combination of PD-1 blockade with radiotherapy and anti-VEGF therapy. Herein, we present safety and efficacy data from a phase 1 study combining pembrolizumab, an anti-PD-1 monoclonal antibody, with hypofractionated stereotactic irradiation (HFSRT) and bevacizumab in recurrent high grade glioma. **METHODS:** This phase I study (3 + 3 design) explored the safety, tolerability, recommended phase II dose (RP2D), and antitumor activity of pembrolizumab administered concurrently with HFSRT and bevacizumab. Adult patients with recurrent glioblastoma or anaplastic astrocytoma (maximum diameter of target lesion ≤ 3.5 cm) were eligible. Eligible patients received HFSRT to the recurrent tumor (30 Gy in 5 fractions) combined with bevacizumab (10 mg/kg, Q2W) and pembrolizumab (100 mg or 200 mg intravenously based on dose level, Q3W). Two dose levels of pembrolizumab were explored and 20 patients were treated at RPD2. Treatment continued until disease progression or unacceptable toxicity. **RESULTS:** Twenty three patients with recurrent glioblastoma have been treated on this study (3 patients at 100 mg and 20 patients at 200 mg dose levels). Five patients had previous tumor progression on bevacizumab. Combination of HFSRT with pembrolizumab (200 mg every 3 weeks) and bevacizumab was generally well tolerated. The most common toxicities were grade 1 fatigue and grade 1 proteinuria. No treatment-related neurologic adverse events were observed. In 1 patient, study treatment was discontinued due to grade 3 elevation of liver transaminases. Durable objective responses (complete response + partial response ≥ 6 months) were observed in 53% of patients. The overall survival rate (at the time of abstract submission) at 6 and 12 months were 94% (16 out of 17 patients) and 64% (7 out of 11 patients), respectively. **CONCLUSION:** Combination of HFSRT with pembrolizumab (200 mg every 3 weeks) and bevacizumab is safe. Clinical activity of this combination therapy is encouraging.

ATIM-19. POPULATION PHARMACOKINETIC (PPK) ANALYSIS OF NIVOLUMAB FLAT AND WEIGHT-BASED DOSING REGIMENS AND ASSOCIATIONS WITH SAFETY IN PATIENTS WITH RECURRENT GLIOBLASTOMA (RGBM) TREATED IN CHECKMATE 143

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BACKGROUND: Nivolumab 3 mg/kg Q2W was well tolerated in rGBM in CheckMate 143 (NCT02017717). It is unknown if nivolumab PK will differ in rGBM vs other tumor types; therefore, a PPK analysis was performed to compare nivolumab PK in patients with rGBM vs those with NSCLC. Additionally, this analysis was used to determine if exposure or safety will differ with flat (240 mg Q2W) vs weight-based dosing (both approved in multiple tumor types) in rGBM. **METHODS:** Nivolumab PK was characterized using samples from patients with rGBM (n=161; CheckMate 143) and NSCLC (n=654; 5 studies). A PPK model incorporating baseline covariates was developed. Post-hoc individual parameters were used to predict exposure with flat vs weight-based dosing. Safety was assessed per CTCAE v4.0. **RESULTS:** Nivolumab PK was well described by a 2-compartment model with time-varying clearance. Baseline clearance was 45% lower in rGBM (0.149 L/d) than in NSCLC (0.271 L/d); magnitude of clearance decrease over time was also lower (8% vs 30%). Nivolumab exposures (steady-state trough serum concentration) were 45% higher in rGBM than in NSCLC (97.2 vs 66.9 ug/mL); similar exposures (100 ug/mL) were predicted with flat dosing in rGBM. Across exposure quartiles (<103.5 [n=37]; ≥103.5–<117.1 [n=39]; ≥117.1–<131.2 [n=37]; ≥131.2 ug/mL [n=38]) in rGBM (weight-based dosing), AE incidence (any grade) varied from 94.6% to 97.3%, with the incidence of grade ≥3 AEs being 48.6%, 33.3%, 51.4%, and 52.6%, respectively. **CONCLUSIONS:** Nivolumab exposures were higher in rGBM than in NSCLC, which has exposures similar to melanoma and RCC, but were within the range evaluated and considered safe in a dose-escalation study (NCT00730639). Increased nivolumab exposure in rGBM was not associated with an increase in grade ≥3 AEs. Similar exposures were predicted with nivolumab 240-mg and 3-mg/kg Q2W regimens, suggesting that flat dosing is a viable regimen for future GBM studies.

ATIM-20. CLINICAL OUTCOMES WITH IPILIMUMAB IN COMBINATION WITH BEVACIZUMAB IN PATIENTS WITH RECENTLY DIAGNOSED GLIOBLASTOMA - A RETROSPECTIVE COHORT REVIEW

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BACKGROUND: Median survival for patients with glioblastoma remains under a year. Whilst there is accumulating interest in the role of checkpoint inhibitors in newly diagnosed glioblastoma, the results of clinical trials are awaited to establish clinical efficacy. We have previously presented clinical outcomes in patients with relapsed glioblastoma treated with the anti-CTLA-4 monoclonal antibody ipilimumab in combination with the anti-VEGF monoclonal antibody bevacizumab. **METHODS:** We retrospectively identified patients with newly diagnosed WHO grade IV glioma who received treatment with ipilimumab and bevacizumab at our centre between March 2015 and March 2017. Baseline demographics, tumour characteristics, concurrent therapy, radiological responses, and survival data were analysed. **RESULTS:** Nineteen patients were identified, 18 with glioblastoma and one with a glioneuronal tumour (Grade IV). Median age was 52 years (range 22–85) and 79% were male. 5% (1/19) had an IDH mutation, and 38% (6/16) had MGMT promotor methylation. Ipilimumab (3mg/kg, 3 weekly, 4 cycles) and bevacizumab (10mg/kg 2 weekly), given with concurrent G-CSF or GM-CSF were commenced after radiotherapy (except in one patient who did not receive radiotherapy). 58% of patients had prior surgical debulking (42% biopsy only), 79% had prior radical radiotherapy with concomitant temozolomide, 16% had short course radiotherapy, and 5% did not receive radiotherapy. 84% of patients received adjuvant temozolomide, and 89% received concurrent valganciclovir. In those with visible disease on pre-treatment MRI, 62% (8/13) had a radiological response. At time of analysis, 63% of patients remained alive, and 58% were alive and progression free. Median follow up was 15 months. Median survival in patients who had had debulking surgery was 23 months, and median survival in those who had a biopsy only was 16 months. **CONCLUSION:** This combination requires prospective evaluation in clinical trials to formally determine efficacy. Data on this cohort continues to be collected and will be updated.

ATIM-21. INTRAVENOUS DELIVERY OF TOCA 511 IN PATIENTS WITH HIGH GRADE GLIOMA RESULTS IN QUANTIFIABLE EXPRESSION OF CYTOSINE DEAMINASE IN TUMOR TISSUE

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Toca 511 (vocimagene amiretroprepvec) is an investigational, conditionally lytic, retroviral replicating vector that encodes an optimized yeast cytosine deaminase (CD) gene. The CD gene converts the prodrug, Toca FC (investigational, extended-release 5-fluorocytosine), into the chemotherapeutic, 5-FU in infected tumors. In a Phase 1 study (NCT01985256), Toca 511 was injected intravenously for 1, 3, or 5 days to patients with recurrent high grade glioma. Tumors were subsequently resected, and Toca 511 was injected into the resection cavity walls. At the time of resection, tissue from various regions of the tumor was collected and processed for quantitative PCR analysis of CD RNA and DNA. Tissue from corresponding locations was fixed for assessment of CD protein expression by immunohistochemistry (IHC). Expression of CD protein was quantified based

on immunofluorescence signal and was shown to co-localize in cells with detectable levels of gag, a viral structural protein. CD protein expression by IHC was assessed in tissue from locations that corresponded with samples positive for CD by PCR and ranged from 1.16% to 10.4% area of the field. These data show that intravenous delivery of Toca 511 results in appreciable deposition of vector in the tumor. Further, we have observed an inverse correlation between T cell infiltrate in the tumor microenvironment and clinical benefit in a complementary Phase I study in which Toca 511 was solely delivered into the resection cavity. Therefore, the nature of the study design described herein, which uses IV delivery of Toca 511, provides a unique opportunity to assess the spatial relationship between CD protein expression and histological features of the tumor. Immunohistochemical assessment to determine spatial correlates between CD protein and T cells, T regulatory cells, and immunosuppressive myeloid cells will be presented. Updated clinical response data will also be presented.

ATIM-22. ADOPTIVE IMMUNOTHERAPY USING LYMPHOKINE-ACTIVATED AB T-CELLS IMPROVES TEMOZOLOMIDE-INDUCED LYMPHOPENIA IN PATIENTS WITH GLIOMA

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Primary and metastatic malignant brain tumors are intractable cancers for which there are limited treatment options and an extremely poor prognosis, and new therapeutic strategies need to be continuously developed. Many new approaches are currently being investigated for treating malignant brain tumors including glioblastoma multiforme (GBM), among which immunotherapy is very promising and attractive. In this clinical study, we investigated the safety and clinical usefulness of systemic adoptive immunotherapy using autologous lymphokine-activated αβ T-cells (αβ T-cells), combined with standard therapies, in patients with malignant brain tumors. Twenty-three patients with different malignant brain tumors, consisting of 14 treated with temozolomide (TMZ group) and nine treated without temozolomide (non-TMZ group), received systemic intravenous injections of αβ T-cells (mean=10.4 injections/patient for the TMZ group, and 4.78 for the non-TMZ group). No significant adverse effects associated with the αβ T-cell injection were observed, and the total lymphocyte count (TLC) improved significantly in the TMZ group after five injections. Furthermore, CD8-positive or T-cell receptor V gamma -positive cells were increased with TLC in three patients with GBM. These findings suggest that systemic αβ T-cell immunotherapy is well tolerated, and may help restore an impaired and imbalanced T-cell immune status, and temozolomide and/or radiotherapy-induced lymphopenia.

ATIM-23. PHASE I TRIAL OF ANTI-LAG-3 OR ANTI-CD137 ALONE AND IN COMBINATION WITH ANTI-PD-1 IN PATIENTS WITH RECURRENT GBM

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BACKGROUND: Given the success of immunotherapy in other solid tumors, immunotherapy is being actively investigated in GBM. Preclinical data with the checkpoint molecules anti-Lag-3 and anti-CD137 have effectively induced an anti-tumor immune response with resultant improved survival when combined with anti-PD-1. **METHODS:** The Adult Brain Tumor Consortium (ABTC) 1501 trial is a phase I, open label, multicenter, multi-arm dose-finding/safety study of anti-LAG-3 (BMS-986016) or anti-CD137 (BMS-663513) alone and in combination with anti-PD-1 in patients at first recurrence of GBM. The primary objective is to define MTD for the mono and combinational treatment. The major secondary objective is to explore for a signal in efficacy. The key inclusion criteria are adults, first recurrence of GBM following RT+TMZ, TLC≥1000/ul, KPS≥ 60%, stable corticosteroid regimen, measurable disease, and written informed consent. Sequential allocation is used for the treatment assignment at starting dose of 80mg for anti-LAG-3 and 8mg for anti-CD137. Anti-PD-1will be given at a flat dose of 240 mg in the combination treatment arms. The 3 + 3 design is used for the dose finding with a target DLT rate ≤ 33%. **RESULTS:** 7 patients have been enrolled in the initial single dose arms with an average age at 60 and KPS at 80%. Three patients were treated with anti-LAG-3 at 80 mg and 4 patients were on 8mg anti-CD137. One patient had a grade 2 headache attributed to anti-CD137. There were a grade 2 fatigue and a grade 3 leukocytosis attributed to anti-LAG-3. No DLT was observed. **CONCLUSIONS:** The trial is ongoing. The first dose of both anti-LAG-3 and anti-CD137 were well tolerated. The single agent arms and a combination arm with anti-PD-1 are open for accrual.

ATIM-24. TARGETING MYELOID DERIVED SUPPRESSOR CELLS: PHASE 0/1 TRIAL OF LOW DOSE CAPECITABINE + BEVACIZUMAB IN PATIENTS WITH RECURRENT GLIOBLASTOMA

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BACKGROUND: Glioblastoma creates an immunosuppressive environment that allows tumor growth. Myeloid derived suppressor cells (MDSCs), a class of immunosuppressive cells, mediate immunosuppression in GBMs. MDSCs are up-regulated in the blood of GBM patients. We have developed a novel strategy to target GBM immunosuppression using low dose 5-fluorouracil (5-FU) to target MDSCs. Marked MDSC depletion occurs at 5-FU doses in mice equivalent to <10% of the normal human dosing. Goal: proof of concept that MDSC suppression is feasible in GBM patients with low-dose capecitabine, an oral analogue of 5-FU. Methods: Eligibility: Recurrent GBM in need of surgical resection; no prior capecitabine or bevacizumab. Cohorts of 3–6 patients receive low-dose capecitabine 150 mg/m2/d (dose level [DL] 1) for 7 days pre-surgery. Post-op, patients resume capecitabine for one cycle after which bevacizumab is added. Concentrations of blood MDSCs, immune cell, and relevant secreted factors are measured at baseline; pre- and post-op; and after the addition of bevacizumab. Tumors are assayed for MDSCs and glioma stem-like cells (GSCs). Primary endpoint: MDSC and T-Regulatory cell reduction after capecitabine. Secondary endpoints: Tumor concentrations of MDSCs, GSCs, and regulatory T-cells (T-regs); safety; and PFS6. Results: Six patients have enrolled to date; data are available on 4. On DL1, MDSC reductions (range 12–28%) from baseline have not yet reached goal of 90%. T-regs fell slightly (range 0–12%). Cytotoxic T-cell (CTL) concentrations rose significantly (5, 28, 86, and 93%). No patient experienced grade 3 or higher toxicity. Two treatment-related SAEs (hemorrhage, non-neutropenic fever) have occurred. Conclusions: In the initial cohort, low dose capecitabine was associated with a modest reduction in MDSCs and a significant increase in CTLs. Toxicity has been minimal. One of 3 evaluable patients has reached 6 months free of progression. Dose escalation continues. (NCT02669173) (Supported by Musella Foundation, Blast GBM, Sontag Foundation, Velosano, Mylan Pharmaceuticals)

ATIM-25. IMMUNOLOGICAL ACTIVATION IN RESPONDING PATIENTS WITH RECURRENT HGG AFTER TREATMENT WITH TOCA 511 & TOCA FC: RESULTS FROM A PHASE 1 TRIAL

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A dose-escalation clinical study (NCT01470794) using a retroviral replicating vector (RRV), Toca 511 (vocimagene amiretrorepvec), in combination with oral Toca FC (extended-release 5-fluorocytosine, 5-FC) is ongoing to evaluate safety, mechanism of action, and preliminary efficacy of this investigational therapy in patients with recurrent HGG. Toca 511 encodes a yeast-derived, codon-optimized, heat-stabilized cytosine deaminase that converts 5-FC to the anti-cancer drug 5-FU in infected tumors. This virus replicates selectively in malignant tissue and may have broad application in cancer therapies. When Toca FC is administered, cytosine deaminase is designed to convert 5-FC to 5-FU resulting in cancer cell death. In preclinical tumor models, as infected cancer cells are killed, diffusible 5-FU also kills susceptible cells, including myeloid derived suppressor cells that contribute to immune-suppression in the tumor