Title

ATIM-14. ALLIANCE A071101: A PHASE II RANDOMIZED TRIAL COMPARING THE EFFICACY OF HEAT SHOCK PROTEIN PEPTIDE COMPLEX-96 (HSPPC-96) VACCINE GIVEN WITH BEVACIZUMAB VERSUS BEVACIZUMAB ALONE IN THE TREATMENT OF SURGICALLY RESECTABLE RECURRENT GLIOBLASTOMA

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resected newly diagnosed GBM who had completed radiation/concurrent temozolomide were enrolled. DC's were generated in vitro from patients' CD14+ monocytes with an optimized technique for DC maturation. Vaccines were generated by pulsing autologous DC's with allogeneic tumor lysate from two allogeneic patient-derived human GBM cell cultures with defined tumor antigen expression. Patients received temozolomide plus vaccine for up to 6 cycles followed by vaccine alone for up to 6 cycles. **RESULTS:** Patients enrolled were relatively enriched for poor prognostic factors (45% subtotal resection, 25% multifocal, 20% bilateral, 95% IDH wild type, 70% MGMT promotor unmethylated). Vaccine manufacture was successful (≥ 15 doses of mature, > 70% CD83+ DC's) in all patients. Treatment has been well tolerated with only grade 1 – 2 toxicities (fever, rash, fatigue) potentially related to the vaccine. Increased circulating tumor-associated antigen-specific CD8 T-cells have been demonstrated post-vaccination with dextramer flow cytometry. Median OS was 20.5 months and PFS was 9.7 months. 30% of patients remain progression-free at nearly 3 years. **CONCLUSIONS:** Autologous mature DC/allogeneic tumor lysate vaccines in combination with temozolomide are safe, feasible, and generates tumor antigen-specific immune responses in newly diagnosed GBM patients. Median OS and PFS are relatively prolonged compared to historical controls, particularly in light of poor baseline prognostic factors. More intriguing is a prolonged tail of progression-free survival in almost one third of patients

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BACKGROUND: Heat shock protein vaccines can be used to stimulate anti-tumor immune responses. An autologous vaccine (HSPPC-96) generated from patient resected tumors has been previously studied in single arm phase I/II trials for newly diagnosed and recurrent GBM. Based on promising survival in these studies, a randomized, multi-centered phase II trial of HSPPC-96 for recurrent GBM compared to bevacizumab was undertaken (NCT01814813). **METHODS:** Patients with 1st/2nd recurrence of resectable GBM were enrolled and underwent surgery with generation of HSPPC-96 from autologous tumors. Post-operative eligibility included a volumetric extent of resection ≥90% (by central review) and sufficient tumor to generate a minimum of 4 vaccine doses. Patients were randomized (1:1:1) to receive HSPPC-96 vaccine followed by bevacizumab at subsequent progression vs. concurrent HSPPC-96 vaccine and bevacizumab vs. bevacizumab alone. The primary endpoint was overall survival (OS) aiming to detect a 36% reduction in HR with 85% power and alpha=0.1 for pooled HSPPC-96 groups vs. bevacizumab alone. Planned enrollment was 165 patients (n=55/arm). An interim analysis was pre-planned at 50% of events (65 deaths). Secondary endpoints included progression-free survival and adverse events. **RESULTS:** At final analysis, 90 patients were enrolled with a distribution of 29:30:31. The study was terminated for futility after the interim analysis. In the intention to treat population, OS for the HSPPC-96 treated groups was 7.5 vs. 10.7 months for bevacizumab alone (HR=2.06 [95% CI 1.18–3.60], p=0.008). Among patients treated per protocol (n=73), OS for HSPPC-96 patients was 8.6 vs. 12.3 months (HR=1.99 [95% CI 1.03–3.81], p=0.03). Trends were similar for progression-free survival between groups. HSPPC-96 toxicity was well tolerated with no attributable serious adverse events. **CONCLUSIONS:** The study failed to demonstrate a survival benefit for patients treated with HSPPC-96 alone or in combination with bevacizumab compared to bevacizumab alone. Correlative analyses are ongoing. SUPPORT: U10CA180882, U10CA180821, U10CA180868, U24CA196171.

ATIM-16. MRI-GUIDED CONVECTIVE DELIVERY OF MDNA55, AN INTERLEUKIN-4 RECEPTOR TARGETED IMMUNOTHERAPY FOR THE TREATMENT OF RECURRENT GLIOBLASTOMA

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Intratumoral glioblastoma therapy has been limited by suboptimal spatial distribution of therapeutic agents. MR-guided convection-enhanced delivery (CED) of MDNA-55 (interleukin-4 fused to Pseudomonasexotoxin) is underway in a Phase 2 open-label study in up to 43 patients with recurrent glioblastoma. Gadolinium-based contrast agent (Gd-DTPA) is co-infused with MDN55 to optimize intra-tumoral catheter placement, monitor drug distribution and identify non-functional catheters. MR images acquired prior to, during, and following infusion are used to determine drug distribution, tissue response, and disease status. Depending on the tumor size up to 60 mL of MDNA55 at a concentration of 1.5 µg/mL is administered as a single infusion through each catheter for a maximum dose of 90 µg. We report preliminary results of tumor distribution in 6 subjects that underwent MR-guided delivery of MDNA55 via implantable flexible catheters. Target enhancing tumor volume varied between 1.5 to 24 mL and tumor diameter varied between 1.8 to 4.7cm. Volume of infusion ranged between 14 to 66 mL and was delivered via 1 to 3 catheters at a flow rate of up to 15mL/min per catheter. MR was employed to monitor initial infusion, allowing adjustment of catheter depth as needed. The bulk of the delivery was performed outside the MR scanner in awake patients. MR confirmation of the distribution was performed within 4 hours post-infusion. In all patients, remarkable tumoral and peri-tumoral distribution has been observed. Tumor coverage ranged from 43% to 100%. Ratio of volume of distribution (Vd) to the volume infusion (Vi) ranged from 2.2 to 0.6. Lower Vd/Vi ratios were associated with drug leakage into the CSF space and/or resection cavity. When catheter placement was inaccurate, real-time imaging of Gd-DTPA distribution enabled adjustments to catheter depth which dramatically improved tumor coverage. MR-guidance during CED is therefore critical for optimal drug distribution in brain tumors.

ATIM-17. EARLY RESULTS OF A MULTICENTER PHASE I AND OPEN-LABEL, RANDOMIZED PHASE II STUDY TESTING THE TOXICITIES AND EFFICACY OF MK-3475 (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. The primary endpoint is PFS. 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. As of 5/16/17, there was no dose-