Title

ATIM-38. PHASE 2 STUDY TO EVALUATE THE CLINICAL EFFICACY AND SAFETY OF MEDI4736 (DURVALUMAB, DURVA) + BEVACIZUMAB (BEV) IN BEV-NAÏVE PATIENTS WITH RECURRENT GLIOBLASTOMA (GBM)

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in the concurrent safety run-in phase. 2 dose-limiting toxicities (DLT) were observed in 1 patient who developed both grade 3 hepatitis and pneumonitis related to atezo. 2 patients discontinued treatment during the concurrent stage due to medical complications deemed unrelated to study drug. In the 8 evaluable patients who completed the concurrent phase, no other grade 3 or 4 atezo-related toxicities were observed. 5 of the 8 evaluable patients completed the combination treatment without the need for dexamethasone. The remaining 3 of the 8 evaluable patients required no more than 4 mg daily of dexamethasone during combination treatment. All 8 patients had stable MRI findings following completion of the concurrent phase. 7 of the 8 evaluable patients proceeded with adjuvant treatment with atezo and TMZ with no grade 3 or 4 atezo-related toxicities observed to date (no. cycles range, 1–6). CONCLUSIONS: Concurrent use of atezo with radiation and TMZ was tolerable, and no new safety signals were noted. The majority of evaluable patients were able to complete the combination treatment without the need for concurrent steroid administration. The phase II component of the trial is recruiting patients (n=50) to evaluate clinical efficacy.

ATIM-38. PHASE 2 STUDY TO EVALUATE THE CLINICAL EFFICACY AND SAFETY OF MEDI4736 (DURVALUMAB, DURVA) + BEVACIZUMAB (BEV) IN BEV-NAÏVE PATIENTS WITH RECURRENT GLIOBLASTOMA (GBM)

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BACKGROUND: Durva is a human IgG1 mAb against PD-L1. Blockade of PD-1/PD-L1 has shown benefit among solid tumors; data implicate PD-1/PD-L1 signaling as a significant contributor to immunosuppression in GBM. BEV is an approved angiogenesis inhibitor for recurrent GBM; angiogenesis inhibition may promote antitumor benefit of immunotherapies. A review showed that lower dose BEV resulted in longer PFS/OS than the standard. METHODS: Ongoing Phase 2 open-label study (NCT02336165) evaluates safety and efficacy of durva (10mg/kg Q2W) in 5 GBM cohorts. Results are presented for Cohorts B2 (durva + BEV 10mg/kg Q2W) and B3 (durva +BEV 3mg/kg Q2W) in BEV-naïve recurrent GBM. Primary efficacy endpoint for Cohorts B2/B3 is 6-month progression-free survival (PFS6), by modified RANO per investigator assessment; secondary endpoints include safety/tolerability. Comparative benchmark for BEV in recurrent GBM is PFS6 of 42%. The null hypothesis (PFS6 ≤42%) was tested in Intent-to-Treat (ITT) population against the alternative hypothesis (PFS6 ≥62%). ITT includes patients receiving any dose of durva and having at least baseline and 1 post-baseline tumor assessment. Durva alone in Cohort B of this study demonstrated PFS6 of 20% (90% CI: 9.7, 33.0). RESULTS: As of 02Apr2018, 33 patients were treated in each cohort (B2, male: 54.5%, median age: 57.0 [40–74] years; B3, male: 60.6%, median age: 54.0 [23–73] years). Most common treatment-related adverse events (TRAEs, in ≥4 [12.1%] patients in either cohort): fatigue, dysphonia, increased ALT, AST, amylase, or lipase, diarrhea, hypertension, arthralgia, headache, and proteinuria. Incidences of TRAEs by maximum CTCAE grade (Gr) ≥3 for Cohorts B2/B3 were Gr3: 24.2/6.1%; Gr4: 0/6.1%; and Gr5: 0/0%. Kaplan-Meier estimate for PFS6 (n=33 each): B2, 15.2% (80% CI: 8.2, 24.0); B3, 21.1% (80% CI: 12.4, 31.4); 3 patients in each cohort showed partial response. CONCLUSIONS: The addition of durva to BEV did not improve on the outcome of durva alone.

ATIM-39. IMPROVED SURVIVAL NOTED IN GLIOBLASTOMA PATIENTS TREATED WITH ADJUVANT TLR-3 AGONIST IN SETTING OF AUTOLOGOUS LYSATE-PULSED DC VACCINATION

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Despite advances in the understanding of glioblastoma multiforme (GBM) molecular biology, genomics, and tumor microenvironment, prognosis for patients diagnosed with this disease remains dismal with standard therapies. We and others have shown utility in dendritic cell (DC) vaccination as an active immunotherapeutic treatment for these patients. In this study, we evaluated the use of autologous tumor lysate puled DC vaccine with and without adjuvant toll-like receptor (TLR) agonists. TLRs are present on dendritic cells and serve to modulate immune responses. Twenty-three patients with WHO Grade III or IV glioma were treated with three intradermal injections of autologous tumor lysate-pulsed DC on days 0, 14, and 28 followed by adjuvant placebo treatment, resiquimod (TLR-7 agonist), or poly ICLC (TLR-3 agonist). Gene expression profiling, immunohistochemistry, and mass cytometry (cyTOF) were performed on patient tumors and peripheral blood mononuclear cells. Patients that received adjuvant poly ICLC had a significantly improved median survival of 54 months over placebo (11 months) and adjuvant resiquimod (17 months) groups. Within each treatment cohort, patients with Grade III tumors had increased overall survival over Grade IV tumors. Overall, patients with MGMT methylated tumors on pathology had a median survival of 57 months, while patients with MGMT unmethylated tumors had a median survival of 19 months. Our findings suggest that adjuvant TLR-3 agonist improves outcomes with autologous lysate-pulsed DC vaccine treatment.

ATIM-40. HIGH RATE OF OBJECTIVE ANTI-TUMOR RESPONSE IN 9 PATIENTS WITH GLIOBLASTOMA AFTER VIRO-IMMUNOTHERAPY WITH ONCOLYTIC PARVOVIRUS H-1 IN COMBINATION WITH BEVACICUMAB AND PD-1 CHECKPOINT BLOCKADE

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BACKGROUND: Combination therapy is an emerging concept to improve the clinical effects of oncolytic virus based anti-cancer strategies. In a phase I/IIa trial (ParvOryx01) the oncolytic H-1 parvovirus (H-1PV) induced markers of immune activation in patients with recurrent glioblastoma. The goal of this investigation was to enhanced H-1PV efficiency by combination treatment with immune modulators, namely bevacicumab and checkpoint blockade. Methods: 9 patients (age 29 to 69 years) with primary (n=2) or recurrent (n=7) glioblastoma were treated in a compassionate use (CU) program with a combination of H-1PV followed by bevacicumab and PD-1 blockade. 7 of the patients received both intratumoral and intravenous injection of H-1PV and 2 patients only intravenous virus treatment. GMP-grade H-1 virus and medication was provided by Oryx GmbH&Co KG, Baldham, Germany) on a humanitarian basis. MRI was analyzed by an independent neuroradiologist to determine objective tumor response rate (ORR) applying RANO criteria. RESULTS: Objective tumor response was observed in 7 of 9 patients (78%). Two patients showed complete responses (22%), 5 patients had partial remissions (56%) with tumor reduction between 49% up to 94% and 2 patients progressive disease (22%). Interestingly, both patients with progressive disease showed local anti-tumor responses where virus was injected but developed new lesions. The treatment was well tolerated and lead to clinical improvement in all symptomatic patients (n=5). CONCLUSION: H-1PV based viro-immunotherapy lead to ORR in 78% of glioblastoma patients. This is a much higher response rate than reported for treatment with either bevacizumab or checkpoint blockade and it supports further systematic clinical development of this novel concept for malignant glioma therapy.

ATIM-41. PHASE II TRIAL OF A SURVIVIN VACCINE (SurVaxM) FOR NEWLY DIAGNOSED GLIOBLASTOMA

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BACKGROUND: Survivin is an anti-apoptotic protein that is highly expressed in glioblastoma (GBM). We conducted a single-arm, multi-center phase II trial in newly diagnosed GBM (nGBM) to determine 6-month progression-free survival (PFS-6), 12-month overall survival (OS-12) and immunologic response in patients treated with surgery, chemoradiation, adjuvant temozolomide (TMZ) and survivin-targeted immunization. METHODS: Patients with nGBM who hadwith HLA-A*02, -A*03, -A*11 and -A*24 haplotypes and, Karnofsky performance status ≥70 were included. Following craniotomy (3 residual contrast enhancement) and chemoradiation, patients received 4 prime-boost doses of SurVaxM (500