BACKGROUND: The EGFR deletion mutation, EGFRvIII, is expressed in ~30% of glioblastomas (GBM). The EGFRvIII-targeted vaccine rindopepimut consists of EGFRvIII peptide conjugated to keyhole limpet hemocyanin (KLH). A survival benefit was observed in a randomized phase 2 trial of recurrent GBM (ReACT; n=70). In three phase 2 studies of 105 total patients with newly diagnosed GBM and minimal residual disease (MRD), the median overall survival (mOS) was 20–22 months, as compared to ~16 months for two matched contemporary datasets (n=16, n=29). METHODS: With newly diagnosed, resected, EGFRvIII+ GBM were, after standard chemoradiation, stratified by RPA class, MGMT promoter methylation, and geographic region, and randomized (1:1) to double-blind rindopepimut or control (KLH) concurrent with standard maintenance temozolomide. Primary endpoint is OS for MRD patients (enhancing tumor <2 cm2 post-chemoradiation by central review) aiming to detect hazard ratio (HR) ≤0.71 with 80% power and alpha=0.05 (log-rank test). Interim analyses were preplanned at 50% and 75% of events. Secondary analyses included patients with ≥2 cm2 of residual tumor (non-MRD). ReACT-2: NCT01582157, ReACT-3: NCT01582143 (403 MRD) were randomized at 165 centers. Data was terminated for futility after the 2nd interim analysis (HR OS 0.99). At final analysis, mOS for rindopepimut vs. control was 20.1 vs. 20.0 (HR=1.01; p=0.93) in the MRD cohort, and 14.8 vs. 14.1 (HR=0.97; p=0.066) with 2-year OS 30% vs. 19% in the non-MRD cohort. There were no substantial differences in progression-free survival. Rindopepimut was well tolerated (chief toxicities: injection site reaction) with robust anti-EGFRvIII immune response. CONCLUSIONS: The study failed to demonstrate a survival benefit for patients treated with rindopepimut and standard chemoradiotherapy. Rindopepimut OS is comparable to prior studies, however, patients in the control arm fared better than historical controls. A trend for long-term survival benefit in non-MRD patients suggests a preferential effect in bulkier disease.

ATIM-04. PHASE 2 STUDY TO EVALUATE THE CLINICAL EFFICACY AND SAFETY OF MED4736 (DURVALUMAB [DUR]) IN PATIENTS WITH Glioblastoma (GBM): RESULTS FOR COHORT B (DUR MONOTHERAPY), BEVACIZUMAB (BEV) NAÏVE PATIENTS WITH RECURRENT GBM

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BACKGROUND: DUR is a human IgG1 mAb against PD-L1. Binding of PD-1/PD-L1 has shown benefit among solid tumors; data implicate PD-1/PD-L1 in glioblastoma (GBM) as well. Adjunctive therapy with DUR monotherapy and/or anti-VEGF agents enhances the activity of DUR monotherapy and may help to overcome resistance. METHODS: This ongoing Phase 2 open-label study (NCT02336165) evaluating the safety and efficacy of DUR monotherapy in 5 GBM cohorts. Each cohort evaluated different methods of DUR administration (intratumoral injection, injection into the cavity wall following resection, and intravenous injection followed by resection) and focused on patients with recurrent GBM (MRD) and newly diagnosed GBM (non-MRD). Each cohort was expected to have 29 evaluable patients at data cutoff (6 cohorts: n=145; cohort A: n=30; cohort B: n=29). Patients were randomized to receive DUR (10 mg/kg Q2W) or KLH concurrent with standard chemoradiation. Anti-PD-1/PD-L1 immune monitoring was conducted. The primary efficacy endpoint for Cohort B is progression-free survival at 6 months (PFS-6), based on modified RANO by investigator assessment; secondary endpoints include safety/toxicity, ORR, PFS-6, mOS, and median OS. RESULTS: Of 157 eligible patients, 154 received at least one dose of DUR and were evaluable for efficacy (PFS, objective response rate [ORR]); 6 were progression free at 6 months. Kaplan-Meier estimate for PFS-6 was 20.0% (90% CI: 9.7, 33.0). ORR: partial response, 5 (16.7%) patients; stable disease, 13 (43.3%). CONCLUSIONS: DUR monotherapy appears to be well tolerated and shows activity in BEV-naive recurrent GBM. Further studies are warranted.

ATIM-05. COMPLEMENTARY CLINICAL AND ANCYLAR DATA FROM 123 PATIENTS WITH RECURRENT HIGH GRADE GLIOMA FROM THREE PHASE 1 TRIALS OF TOCA 511 AND TOCA FC: UPDATE AND JUSTIFICATION FOR A PHASE 2/3 TRIAL

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Toca 511 (vincistatin, 5-azacytosine) is an investigational, conditionally lytic, retroviral replicating vector. The vector infects human cells with selectivity for cancer cells because genome integration is dependent on cell division and viral replication is inhibited by innate and adaptive immune responses, defective in malignant tissues. Toca 511 spreads through cancer cells and stably delivers the gene for an optimized yeast cytokine (scFv, the variable region of a human anti-CD40 monoclonal antibody) that converts courses of the prodrug Toca FC (an investigational, extended-release version of 5-fluorocytosine) into 5-fluorouracil (5-FU). The 3-FU directly kills cancer cells likely leading to activation of antigen presenting cells in the tumor microenvironment. 5-FU can also induce immunity, immunosuppressive myeloid cells and kill them, leading to further activation of the immune system against the tumor by removing an important inflammatory brake. The safety, viral kinetics, immune response, and preliminary efficacy of Toca 511 and Toca FC have been investigated since 2010 in three, open-label, ascending dose, Phase 1 studies of 123 patients with recurrent high grade glioma (rHGG), each evaluating different methods of Toca 511 administration (intratumoral injection, injection into the cavity wall following resection, and intravenous injection followed into resection cavity wall) followed by multiple courses of oral Toca FC. Results to date include good tolerability; no persistent viremia; successful gene transduction within resected tumors; and median overall survival with stereotactic biopsy needle, resection cavity wall, and intravenous/cavity wall vector injection ranging from 12.1–13.6 months. Analysis of pretreatment resected tumor samples for mRNA expression patterns showed a survival-related signature that otherwise does not correlate with survival in publicly available databases. Preliminary data from these studies supported initiation of a randomized, Phase 2/3 study in patients with rHGG (NCT02414165) in 2015. Updated and pooled safety data, immune response findings, and updated efficacy data for the Phase 1 studies will be presented.