Title

RBTT-03. A PHASE 1, MULTICENTER, RANDOMIZED, OPEN-LABEL, PERIOPERATIVE STUDY OF AG-120 (IVOSIDENIB) AND AG-881 IN PATIENTS WITH RECURRENT, NONENHANCING, IDH1-MUTANT, LOW-GRADE GLIOMA

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RANDOMIZED BRAIN TUMOR TRIALS IN DEVELOPMENT

RBTT-01. RANDOMIZED PHASE 2 OPEN LABEL STUDY OF NIVOLUMAB PLUS STANDARD DOSE BEVACIZUMAB VERSUS NIVOLUMAB PLUS LOW DOSE BEVACIZUMAB IN RECURRENT GLIOBLASTOMA

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BACKGROUND: The outcome for glioblastoma (GBM) remains dismal with a median survival of 15 months. Vascular endothelial growth factor (VEGF) is a highly upregulated proangiogenic growth factor in GBM that contributes to tumor-associated immunosuppression by inhibition of dendritic cell maturation and antigen presentation, induction of apoptosis of CD8+ T cells and enhancing Treg activity. Hence, a combination of anti PD1 and anti VEGF is promising approach in recurrent GBM. Lower anti-VEGF therapy dosing can lead to enhanced immune infiltrate and improved survival following co-administration with an anti-tumor immunotherapeutic in preclinical studies. METHODS: This is a 90 patient randomized phase 2 open label study of nivolumab plus standard dose bevacizumab versus nivolumab plus low dose bevacizumab in recurrent GBM. Primary endpoint is to evaluate the efficacy of nivolumab when administered with standard and reduced dose bevacizumab as measured by overall survival (OS) at twelve months (OS-12). Secondary endpoint include safety, Progression free survival at 6 months, OS and overall response rate. Exploratory endpoints include circulating immunologic biomarkers, cytokines, archival tumor PD-L1 expression and inflammatory gene expression signature and perfusion and diffusion weighted imaging with response (RANO and iRANO). Eligibility Criteria include Age ≥ 18 years, first recurrence of GBM, normal organ function, KPS ≥ 70. Key exclusion criteria include active, known or suspected autoimmune disease, contraindications for bevacizumab therapy and decadron > 4 mg/day or equivalent of steroids. STATISTICAL ANALYSIS: The one-sample log-rank test will be applied to outcomes observed for each arm individually to test the hypothesis that OS has been improved beyond the null 12-month survival rate of 45%. With N=45 patients per arm, a one-sided test provides power=0.80 to detect survival rate of 58% at 12-months following treatment at the 0.10 significance level. Results: The study (NCT03452579) is ongoing and enrolling GBM patients in first recurrence.

RBTT-02. ENHANCING VACCINE RESPONSES WITH DOSE-INTENSIFIED TEMOZOLOMIDE IN GLIOBLASTOMA: INITIATION OF THE I-ATTAC TRIAL

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Two of our previous clinical trials targeting Cytomegalovirus (CMV) protein pp65 in newly diagnosed glioblastoma (GBM) using pp65-specific dendritic cell (DC) vaccines have yielded long term survival rates greatly exceeding those predicted with standard of care. In the ATTAC trial (IND 12839), patients received sequential DC vaccination throughout monthly cycles of standard temozolomide (STD-TMZ) 200mg/m^2/d for 5d and were randomized to one of two vaccine site preconditioning regimens. Significantly higher rates of DC migration (p=0.04) and survival (p=0.013) were observed in patients randomized to tetanus preconditioning, with half of the cohort living to nearly five years after diagnosis. In the ATTAC-GM trial, we treated a subsequent cohort with dose-intensified TMZ (DI-TMZ) 100mg/m^2/d for 21d prior to and throughout vaccination with GM-CSF-containing DC vaccines and observed extraordinarily prolonged progression-free survival (PFS) and overall survival (OS) (median 25.3 and 41.1 months, respectively). In this trial, DI-TMZ-induced lymphopenia facilitated homeostatic expansion of pp65 responses after an initial DI-TMZ cycle but later ablated T cell responses when monthly cycles were reintroduced. The benefit of DI-TMZ thus warrants further study in a larger series of patients. Here we describe the initiation of a validation trial, "I-ATTAC: Improved Anti-Tumor Immunotherapy Targeted Against Cytomegalovirus in Patients with Newly-Diagnosed WHO Grade IV Unmethylated Glioma" (IND-16301). This prospective single arm Phase 2 trial of 48 patients will validate our findings that tetanus preconditioning and GM-CSF in conjunction with pp65-DCs extends OS in patients with newly diagnosed, unmethylated GBM. By withholding additional TMZ cycles in this patient population, we hypothesize that CMV immune responses will not be abrogated as previously observed, and that this greater expansion will translate into further prolonged survival (primary objective). A series of secondary objectives will be evaluated for the association between increased DC migration, systemic mediators of tetanus preconditioning, and T cell polyfunctionality with survival.

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Mutations in isocitrate dehydrogenase (mIDH) are common in lower-grade glioma (LGG; mIDH1, 80%; mIDH2, 4%) and lead to epigenetic and genetic changes that promote oncogenesis via production of the oncometabolite 2-hydroxyglutarate (2-HG). AG-120 (ivosidenib) is a first-in-class oral mIDH1 inhibitor associated with a favorable safety profile in an ongoing phase 1 study in 66 glioma patients. AG-881 is a brain-penetrant oral mIDH1/2 inhibitor with an acceptable safety profile at dose levels <100 mg in an ongoing phase 1 study in 52 glioma patients. In an orthotopic mIDH1-R132H glioma model, ivosidenib and AG-881 suppressed 2-HG by 85% and 98%, respectively. This multicenter, open-label, phase 1 study is designed to measure brain tumor 2-HG concentration and drug exposure at two dose levels each of ivosidenib or AG-881 in patients with mIDH1 LGG undergoing craniotomy (NCT03343197). The study will enroll ~45 adults with recurrent WHO 2016-classified Grade 2 or 3 mIDH1 oligodendroglioma/astrocytoma eligible for resection. Key eligibility criteria include: nonenhancing disease by T2 FLAIR MRI, mIDH1-R132H, and Karnofsky Performance Score 60. Cohort 1 patients will be randomized 2:2:1 to 500 mg QD ivosidenib (n=10), 50 mg QD AG-881 (n=10), or no treatment (n=5). Based on the safety, 2-HG, and pharmacokinetic data from cohort 1, cohort 2 may enroll an additional 20 patients randomized 1:1 to 250 mg BID ivosidenib or 10 mg QD AG-881. Patients randomized to either drug will receive treatment for 4 weeks preoperatively and may continue treatment after surgery. Untreated patients can opt to be randomized to either drug postoperatively. The primary endpoint is 2-HG concentration in surgically resected tumors. Secondary endpoints include safety, tumor and plasma pharmacokinetics, and RANO LGG response. Exploratory endpoints include 2-HG and pharmacokinetics in cerebrospinal fluid, and 2-HG magnetic resonance spectroscopy. This study is currently enrolling in the USA.

RBTT-04. DOES EXERCISE IMPROVE PROGRESSION FREE SURVIVAL AND QUALITY OF LIFE IN PATIENTS WITH GLIOBLASTOMA? A TRIAL IN PROGRESS

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BACKGROUND: Glioblastoma is the most common adult malignant glioma, with poor prognosis and adverse neurological sequelae. Physical activity improves outcomes in patients with other cancers, but has not been evaluated in GBM. This prospective, single-arm intervention trial examines