Title

ATIM-28. PHASE 2 STUDY OF ERC1671 PLUS BEVACIZUMAB VS BEVACIZUMAB PLUS PLACEBO IN RECURRENT GBM INTERIM RESULTS AND CORRELATIONS WITH CD4+ T LYMPHOCYTE COUNTS

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antitumor immune responses that can be adoptively transferred to untreated animals. In an ascending dose trial (NCT01470794) in patients with recurrent high grade glioma (rHGG), Toca 511 was injected into the resection cavity walls at the time of resection, and then multiple courses of oral Toca FC were administered. Multiyear durable and complete responses by independent radiology review have been reported. Human immune monitoring results support an immunologic mechanism of action and identify potential biomarkers related to patient outcomes. Measurements included the quantification of peripheral blood and tumor infiltrating leukocyte subsets by flow cytometry, immunohistochemistry, and deconvolution of DNA and RNA sequencing data. In addition, systemic cytokine levels were assessed in peripheral blood serum by multiplex digital ELISA. Univariate comparisons and multivariate models revealed immunologic trends associated with patient outcomes. Pre-treatment tumor infiltrating cell subsets, quantified via deconvolution of RNA sequencing data, were associated with both objective responses and survival. Subsequent exploratory models applied to selected patient data indicate that a combined biomarker using mRNA signatures from multiple leukocyte subsets may predict patient outcomes with high sensitivity and selectivity. In addition, post-treatment serum cytokine time-course results suggest that differences and temporal modulations are associated with both objective response and survival. These results support an immune-related mechanism of action for the Toca 511 & Toca FC regimen. Potentially predictive and/or prognostic biomarkers of patient outcomes will be evaluated in the ongoing randomized Phase 3 Toca 5 trial in patients with rHGG (NCT02414165).

ATIM-27. INTRATUMORAL ADMINISTRATION OF AN ONCOLYTIC POLIO/RHINOVIRUS RECOMBINANT (PVSRIPO) IN MALIGNANT GLIOMA PATIENTS: ASSESSMENT OF MUTATIONAL RESPONSE CORRELATES

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BACKGROUND: The live attenuated oral poliovirus vaccine was modified to contain a heterologous internal ribosomal entry site stemming from human rhinovirus type 2, creating PVSRIPO. PVSRIPO recognizes CD155, an oncofetal cell adhesion molecule and tumor antigen widely expressed ectopically in malignancy. We report results of the dose finding trial evaluating PVSRIPO delivered intratumorally by convection-enhanced delivery (CED). METHODS: Eligible patients were adults with recurrent supratentorial WHO grade IV MG; solitary tumor 1–5.5cm in diameter; 4 weeks after chemotherapy, bevacizumab or study drug; adequate organ function; KPS70%; and positive anti-polio titer. RESULTS: A total of 61 pts were treated on study. Only one DLT was observed, a grade 4 intracranial hemorrhage at the time of catheter removal on DL5. Study related adverse events consisted of localized peritumoral inflammation, triggering neurologic symptoms in relation to the location of the infused tumor. Of the 26 patients treated more than 36 months ago, six are alive at 73.6+, 72.5+, 60.6+, 44.0+, 39.3+, and 36.9+ months. Deep sequencing of biopsy material obtained prior to PVSRIPO infusion in 31 samples, confirmed that a very low mutational load is associated with longer survival (p=0.017). Additionally, no patients whose tumors had >0.5 non-synonymous mutations per Mb survived beyond 18 months. CONCLUSION: Infusion of PVSRIPO via CED is safe and encouraging efficacy results were observed in adults along with mutational correlates of response.

ATIM-28. PHASE 2 STUDY OF ERC1671 PLUS BEVACIZUMAB VS BEVACIZUMAB PLUS PLACEBO IN RECURRENT GBM INTERIM RESULTS AND CORRELATIONS WITH CD4+ T LYMPHOCYTE COUNTS

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BACKGROUND: ERC1671 is an allogeneic/autologous therapeutic glioblastoma (GBM) vaccine composed of whole, inactivated tumor cells mixed with tumor cell lysates derived from the patient and three GBM donors. Previously published compassionate use data showed an overall survival (OS) of 43 weeks (10 months) in patients with a good performance status. METHODS: In this double-blinded, randomized, phase 2 study bevacizumab-naïve patients with recurrent GBM were randomized after surgery to receive either ERC1671 in combination with GM-CSF and cyclophosphamide plus bevacizumab, or placebo plus bevacizumab. The trial is registered with ClinicalTrials.gov (NCT01903330). Interim RESULTS: Nine patients, with a KPS 70, were randomized and treated. At the time of further progression, these patients were unblinded, as stipulated by the protocol, which revealed that four had received vaccine, four had received placebo, and one was non-evaluable. Median OS of patients treated with ERC1671 plus bevacizumab was 12 months, with one patient surviving >2 years. In the group treated with placebo plus bevacizumab, median OS was shorter at 7.5 months, with all patients having succumbed within 1 year. Toxicity analysis showed an equal distribution of adverse events (AE) between the vaccine and placebo groups, with no grade 4 or 5 toxicities. The maximal CD4+ T lymphocyte count in the peripheral blood correlated with OS in the ERC1671 but not in the placebo group. CONCLUSIONS: The addition of ERC1671/GM-CSF/cyclophosphamide to bevacizumab resulted in a potential survival benefit with minimal additional toxicity. The maximal CD4+ T lymphocyte count in the peripheral blood correlated with OS. The study is ongoing with the addition of two other sites.

ATIM-29. NRG BN002: SAFETY DATA FROM A PHASE I STUDY OF IPILIMUMAB (IPI), NIVOLUMAB (NIVO), AND THE COMBINATION FOR NEWLY DIAGNOSED GLIOBLASTOMA (GBM)

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INTRODUCTION: Immune checkpoint inhibitors (ICIs) have demonstrated efficacy in several solid tumors including brain metastases, but single agent ICIs have failed to improve outcome in recurrent (GBM). This study evaluated the safety of anti-CTLA-4 (IPI) and anti-PD-1 (NIVO) ICIs alone or in combination in newly diagnosed GBM during adjuvant temozolomide (TMZ) treatment. METHODS: This phase I study evaluated IPI (3mg/kg), NIVO (3mg/kg), and the combination (1 mg/kg & 3 mg/kg respectively) followed by an expansion cohort for the combined treatment of adults with unifocal, supratentorial newly diagnosed GBM after gross or near total resection. ICIs were given with adjuvant TMZ. The primary endpoint was the dose limiting toxicity (DLT) within 8 weeks of starting ICIs. A standard up-and-down design was used with 6 evaluable patients enrolled at a given dose level; safety defined as 1 or fewer patients with DLTs. RESULTS: Thirty-two patients (31 analyzable; 1 not treated) were enrolled, 6 to each arm and 14 to the expansion cohort. Median age: 54 years (range: 23–74), 68% male and 84% white. Overall, treatment was well tolerated with a 16% rate of Grade 4 events; without increased toxicity of combination ICIs; there were no Grade 5 events. One DLT was seen in each single-agent arm; none in the combination arm. Median follow-up time was 8.4 months (range: 0.5–23.6), 10 had progressed (32%) and 8 had died (26%), 7 due to disease progression and 1 due to pulmonary embolism. CONCLUSIONS: IPI and NIVO are safe and tolerable with similar toxicity profiles noted with other cancers when given with adjuvant TMZ for newly diagnosed GBM. Combination IPI+NIVO is not more toxic than single agents. These results provide necessary safety data for a subsequent efficacy trial to test the combination of ICIs in newly diagnosed GBM. Funding: U10CA180868 and U10CA180822 (NCI).

ATIM-30. HOW TO MONITOR IMMUNOGENIC CELL DEATH IN PATIENTS WITH GLIOBLASTOMA

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