INB-200: PHASE I STUDY OF GENE MODIFIED AUTOLOGOUS GAMMA-DELTA (γδ) T CELLS IN NEWLY DIAGNOSED Glioblastoma (GBM) PATIENTS RECEIVING MAINTENANCE TEMOZOLOMIDE (TMZ): IMMUNOBIOLOGIC CORRELATIVE DATA

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Background Drug Resistant Immunotherapy (DRI) combines an alkylating chemotherapy such as temozolomide (TMZ) to force the upregulation of tumor stress-associated NKG2D ligands while simultaneously treating with gamma-delta (γδ) T cells that are genetically engineered to express O-6-methylguanine-DNA methyltransferase (MGMT) to convey TMZ resistance. We present biologic correlative findings for our ongoing study NCT04165941, a Phase 1 trial assessing the safety of autologous DRI.

Methods Adult newly diagnosed GBM patients undergo resection, apheresis, chemoradiotherapy, and up to six cycles of maintenance-phase TMZ. Cohorts (C) 1, 2 and 3 each receive 1, 3 or 6 intracavitary doses of 1 x 10^7 DRI γδ T cells concomitantly with 150 mg/m^2 of TMZ intravenously on day (D) 1 of each 28-day maintenance cycle. Peripheral blood is obtained for immunophenotyping and cytokine analysis at apheresis and at 30, 60, 90, 180, and 365 days following the first infusion. Peripheral blood RCL is assessed at 30, 90, 180 and 365 days following first infusion.

Results Resected primary tumors showed scarce immune cell infiltration with occasional perivascular cuffing. A small resected recurrent tumor from a C1 patient 148D following DRI γδ T cell treatment revealed widespread infiltration of immune cells, including γδ T cells and 60% necrosis. Infused cellular products contained >70–95% γδ T cells. TMZ-based lymphodepletion is evidenced throughout maintenance phase as peripheral T, B, and NK lymphocyte subsets remained near or below published normal ranges for as long as 365 days. CD8+ T cells predominately expressed a naïve (CD45RA+CD27+) phenotype at the beginning of each cycle. IFN-γ was initially upregulated to initiation of maintenance phase and through Day +365 consistent with lymphodepleting chemotherapy. IL-17A and TNF-α also decrease while other cytokines remain at normal serum concentrations throughout treatment. Evaluable C1 patients surpassed expected median PFS at 8.3, 11.9, 7.4 months and OS of 15.6, 17.7 and 9.6 months respectively. Two C2 patients remain alive and progression free at 24.8 and 20.7 months. Two additional C2 patients died of unrelated cardiovascular events at 5.1 and 8.7 months respectively without progression. One C3 patient has completed 5/6 doses without DLT. Cytokine release syndrome (CRS), or neurotoxicity (ICANS) were not observed.

Conclusions Data demonstrates that single and repeat doses of DRI γδ T cells manufactured and transduced in this protocol show manageable toxicity with continued encouraging trend in PFS. Immunophenotyping and Th1/Th2/Th17 cytokine analysis show maintenance of peripheral lymphodepletion throughout the treatment phase.

Trial Registration Clinical Trials Registration number NCT04165941 at www.clinicaltrials.com

Ethics Approval The trial has been approved by the WCG study #1265787, IRB Tracking Number 20192345. Sponsor is the University of Alabama at Birmingham Neuro-Oncology Program, Sponsor Study Number UAB 1773, Principal Investigator Louis B. Nabors, MD.

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