NT-I7, A LONG-ACTING INTERLEUKIN-7, PROMOTES EXPANSION OF CD8 T CELLS AND NK CELLS AND IMMUNE ACTIVATION IN PATIENTS WITH NEWLY DIAGNOSED HIGH-GRADE GLIOMAS AFTER CHEMORADIATION

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Background Lymphopenia is common after chemoradiation for treatment of high-grade gliomas (HGG) and is associated with reduced survival.¹ Interleukin-7 (IL-7) promotes T-cell maturation and proliferation and is inappropriately low in lymphopenic patients with HGG.² We previously demonstrated that first-in-class long-acting IL-7, NT-I7 (efineptakin alfa), reverses lymphopenia and improves survival in murine glioma models.³ This study reports the correlative immune changes after NT-I7 treatment in patients with newly diagnosed HGG in a Phase I/II clinical trial.

Methods Enrolled patients had newly diagnosed HGG treated with concurrent radiotherapy (RT) and temozolomide (TMZ) plus adjuvant TMZ every 4 weeks. NT-I7 was administered intramuscularly 1 week after completion of RT/TMZ and then every 12 weeks, for up to 4 total doses. Phase I utilized the 3+3 design to identify the maximum tolerated dose (MTD). Phase II is a double-blinded, placebo-controlled study with 10 patients in each arm. Immune profiling of patients from the Phase I study was performed with multiparametric flow cytometry and multiplex cytokine analysis.

Results Phase I was completed with 19 patients. The most common adverse events were grade 1 or 2 injection site reactions (42%). Two patients had dose-limiting toxicities at 960 µg/kg (grade 3 elevated alanine aminotransferase and grade 3 back pain), prompting the selection of MTD as 720 µg/kg. Preliminary analysis of Phase I subjects demonstrated dose-dependent increases in absolute lymphocyte count (ALC; 1.3X-4.1X fold increase from pre-therapy measurements) that peaked at week 4, before adjuvant TMZ. Flow cytometry analysis of peripheral blood showed a significant increase in the frequency of CD8+ T-cells, CD4+ T-cells, and CD56bright natural killer (NK) cells after NT-I7 administration. There was no change in B cell counts. Expression of the IL-7 receptor (CD127) was downregulated on most immune subsets within 1 week after NT-I7 administration and recovered to baseline by week 4. Serum cytokine analysis showed a rapid and significant increase in tumor necrosis factor (TNF), chemokine ligand 9 (CXCL9), and a trend to higher interferon-gamma (IFNγ), 1 week after NT-I7 administration.

Conclusions NT-I7 is well tolerated when administered after RT/TMZ for HGG patients. NT-I7 administration prompted an increase in ALC, especially cytotoxic T-cells and NK cells. We also observed rapid increases in key cytokines and chemokines, suggesting immune activation. These findings provide insight into the mechanism of action for NT-I7. Phase II enrollment and additional immune profiling correlates are ongoing.

Trial Registration NCT03687957

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Ethics Approval This study was approved by Washington University's ethics board (the Human Research Protection Office); approval number 201810185. Study participants provided written informed consent.

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