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

Alice Y. Zhou[1], Michael Rettig[1], Jennifer A. Foltz[1], Jingqin Luo[1], Omar H. Butt[1], Chandini Avvaru[1], Ruth G.N. Katumba[1], Albert H. Kim[1], Gavin P. Dunn[1], Christopher Abraham[1], Se Hwan Yang[2], Jean Fan[2], Byung Ha Lee[2], NgocDiep Le[2], George Ansstas[1], Tanner Johanns[1], Jiayi Huang[1], Milan G. Chheda[1], Todd A. Fehniger[1], Jian L. Campian[1,3]

[1]Washington University, St Louis, MO; [2]NeoImmuneTech, Inc., Rockville, MD; [3]Mayo Clinic, Rochester, MN

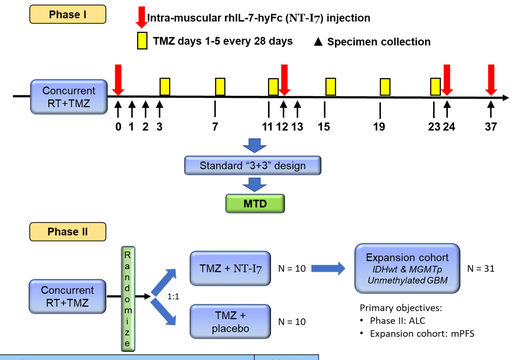
Background

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

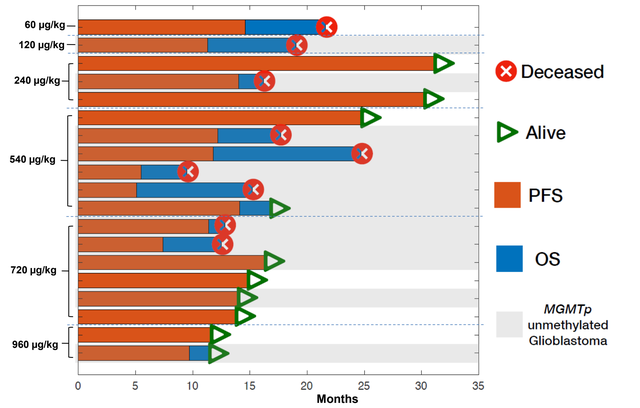
Enrolled patients had newly diagnosed HGG treated with concurrent radiotherapy (RT) and temozolomide (TMZ) plus adjuvant TMZ every 4 weeks. NT-I7 was administered intramuscularly 1 week after completion of RT/TMZ and then every 12 weeks, for up to 4 total doses. Phase I utilized the 3+3 design to identify the maximum tolerated dose (MTD). Phase II is a double-blinded, placebo-controlled study with 10 patients in each arm. Phase I is completed with 19 patients and results are shown here. Immune profiling of patients from the Phase I study was performed on peripheral blood with multiparametric flow cytometry and multiplex cytokine analysis.

Study Design and Enrollment



Demographics	N=19
Age at diagnosis: median (range)	58 (25-78)
Male: No. (%)	14 (74)
Histology	
Glioblastoma: No. (%)	17 (89)
Anaplastic Oligodendroglioma: No. (%)	2 (11)
Genetics	
MGMT methylation status (N=17): methylated No. (%)	5 (29)
IDH mutated: No. (%)	3 (16)
Baseline steroid use: No. (%)	5 (26)

Dose Level	NT-I7 (µg/kg)
1	60
2	120
3	240
4	360
5	540
6	720



Adverse Event	60 µg/kg n=1 (%)		120 µg/kg n=1 (%)		240 µg/kg n=3 (%)		540 µg/kg n=6 (%)		720 µg/kg n=6 (%)		960 µg/kg n=2 (%)	
	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Injection site reaction	1 (100)	0	1 (100)	0	1 (33)	0	2 (33)	0	1 (17)	0	2 (100)	0
Pyrexia	0	0	0	0	0	0	1 (17)	0	0	0	1 (50)	0
Flu like symptoms	0	0	0	0	0	0	2 (33)	0	2 (33)	0	1 (50)	0
Rash	1 (100)	0	0	0	0	0	0	0	0	0	2 (100)	0
Fatigue	0	0	0	0	1 (33)	0	1 (17)	0	0	0	2 (100)	0
ALT increased	0	0	0	0	0	0	2 (33)	0	0	0	1 (50)	1 (50)*
AST increased	0	0	0	0	0	0	2 (33)	0	0	0	0	0
Nausea	0	0	1 (100)	0	0	0	1 (17)	0	1 (17)	0	1 (50)	0
Muscle weakness	0	0	0	0	0	0	1 (17)	1 (17)	2 (33)	0	1 (50)	0
Pain	0	0	0	0	0	0	0	0	0	0	0	1 (50)*

Figure 1. ***Clinical Response and Adverse Events***. The study duration (months) and clinical status of each patient are summarized in the swimming lane plot. Adverse events are listed in the table. Dose-limiting toxicities* were observed at 960µg/kg, and the maximally tolerated dose (MTD) was designated at 720µg/kg. **At the time of the analysis, 4 out of 6 patients receiving the MTD are stable and continue in the study**.

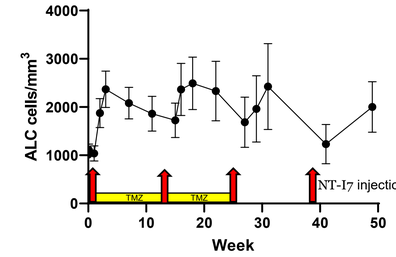


Figure 2. NT-I7 treatment increases peripheral absolute lymphocyte counts (ALC) despite adjuvant TMZ.

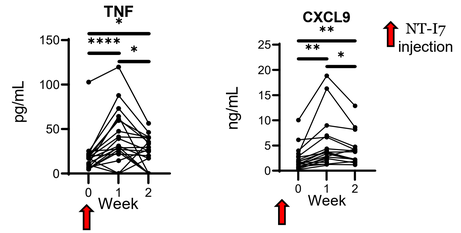


Figure 3. Effect of NT-I7 on cytokine production, with significant increases in TNF and CXCL-9. (*p≤0.05; **p ≤ 0.001; ***p ≤0.0001; ****p ≤0.00001)

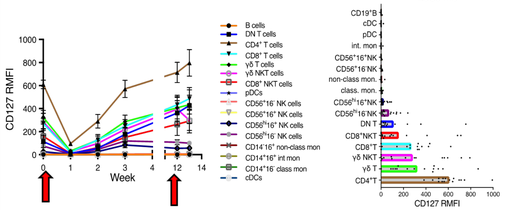


Figure 4. CD127 (IL-7Rα) expression decreased across all cell types by week 1 and recovers to baseline levels by week 4 (*left*). CD127 expression at baseline (*right*).

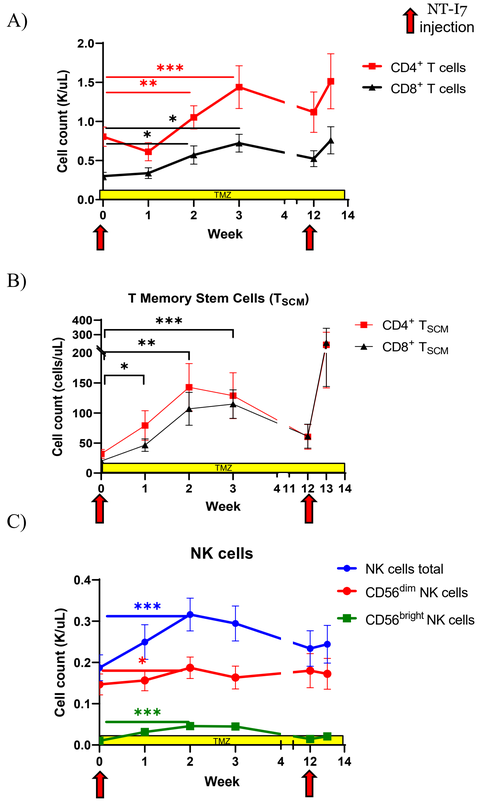


Figure 5. Despite adjuvant TMZ, NT-I7 treatment leads to significant increases in A) CD4⁺ and CD8⁺ T cells and B) the T memory stem cell subset (T_{SCM}). C) NT-I7 treatment also increases NK cell subsets (CD56^{dim} and CD56^{bright} NK cells). (*p≤0.05; **p ≤ 0.001; ***p ≤0.0001; ****p ≤0.00001)

Conclusions

❖NT-I7 is well tolerated in patients with high grade gliomas. The maximum tolerated dose (MTD) was determined at 720µg/kg.
❖NT-I7 increased ALC, especially NK cells and T Memory Stem Cells (T_{SCM}), a self-renewing population with superior antitumor activity when compared to other memory T cell subsets. Additionally, the increases in key cytokines and chemokines suggest immune activation.
❖As expected, CD127 is rapidly down regulated after treatment with NT-I7, likely due to internalization.
❖Phase II enrollment and additional immune profiling correlates are ongoing.

References

1. Mendez et al. Association between treatment-related lymphopenia and overall survival in elderly patients with newly diagnosed glioblastoma. J. Neurooncol. 2016.
2. Campian et al. Pre-radiation lymphocyte harvesting and post-radiation reinfusion in patients with newly diagnosed high grade gliomas. J. Neuro-Oncology 2015.
3. Campian et al. Long-acting recombinant human interleukin-7, NT-I7, increases cytotoxic CD8+ T cells and enhances survival in mouse glioma models. Clin Cancer Res 2021 *Epub ahead of print.*

Contact

Jian L. Campian MD. PhD
campian.jian@mayo.edu

For questions regarding NT-I7, please contact **science@neoimmunetech.com**