A phase I/II study evaluating the safety and efficacy of a novel long-acting interleukin-7, NT-I7, for patients with newly diagnosed high-grade gliomas after chemoradiotherapy

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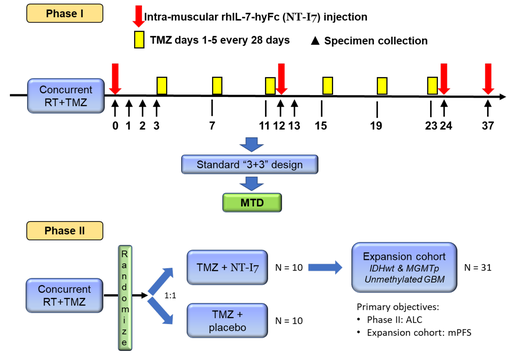
Background

Lymphopenia is common after chemoradiation for 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, increase CD8 T cells in the tumor microenvironment, and improves survival in murine glioma models[3]. We have developed a phase I/II study evaluating the safety and efficacy of NT-I7 in patients with HGG. This study here reports the phase I portion of the study.

Methods

Enrolled patients who had newly diagnosed HGG were treated with concurrent radiotherapy (RT) and temozolomide (TMZ) plus adjuvant TMZ every 4 weeks. NT-I7 was administered intramuscularly within 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 (including an accelerated phase with n=1 for the first 2 doses) 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.

Study Design and Enrollment



Demographics	N=19
Age at diagnosis: median (range)	58 (25-78)
Male: No. (%)	14 (74)
Histology	
Glioblastoma: No. (%)	16 (84)
Anaplastic Oligodendroglioma: No. (%)	2 (11)
WHO Grade 4 Astrocytoma: No. (%)	1 (5)
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	540
5	720
6	960

Results

Pt. ID	NT-I7 (µg/kg)	Age	Sex	Diagnosis	MGMT	IDH	Dex (mg/day)	Cycles received	WBC (cells/mm3)	Hbg (g/dl)	Plt (K/mm3)	ANC (cells/mm3)	ALC (cells/mm3)	CD4 (cells/mm3)
1	60	58	M	GBM	Methylated	WT	0	4	4400	12	225	2900	800	427
2	120	32	M	GBM	Un-Methylated	WT	0	3	4700	13.8	236	3200	900	345
3	240	45	M	AO	Unknown	Mutated	0	4	8300	14.2	131	7400	600	185
4	240	46	M	GBM	Un-Methylated	WT	4	4	7500	15	145	6800	400	171
5	240	67	M	GBM	Methylated	WT	0	4	4700	14.7	125	3700	400	357
6	540	63	M	AO	Unknown	Mutated	0	3	9200	15	395	5900	1900	1181
7	540	67	M	GBM	Un-Methylated	WT	8	1	6500	15	219	5200	600	369
8	540	65	M	GBM	Un-Methylated	WT	0	1	7800	16.5	170	5100	1600	659
9	540	40	F	GBM	Un-Methylated	WT	12	1	5700	13.7	125	4200	1100	386
10	540	64	M	GBM	Un-Methylated	WT	0	1	6100	15.4	321	4100	1000	499
11	540	25	M	GBM	Un-Methylated	WT	2	2	12400	13	261	8300	2000	948
12	720	30	M	GBM	Un-Methylated	WT	0	3	5600	14.8	128	3000	1600	686
13	720	58	F	GBM	Un-Methylated	WT	0	2	6100	13.6	287	4200	1200	853
14	720	58	F	GBM	Un-Methylated	WT	0	4	9300	15.1	285	6400	1700	1030
17	720	58	M	GBM	Methylated	WT	0	2	4300	10.4	307	2200	1100	527
18	720	78	F	GBM	Methylated	WT	0	3	6100	13.4	285	5000	600	359
19	720	66	M	GBM	Un-Methylated	WT	4	2	6100	13.7	327	3700	1000	442
15	960	30	M	Grade 4 Astrocytoma	Methylated	Mutated	0	1	7300	15.2	251	4400	1900	1045
16	960	38	F	GBM	Un-Methylated	WT	0	1	9100	13.9	237	8000	700	292
	Median (range)	58 (25-78)					0 (0-12)	2 (1-4)	6100 (4300-12400)	14.2 (10.4-16.5)	237 (125-395)	4400 (2200-8300)	1000 (400-2000)	442 (171-1181)

Table 1. Patient Characteristics.

n (%)	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	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)

Table 2. Summary of Treatment Related Adverse Events.
* 2 DLTs were seen at 960 µg/kg dose level.

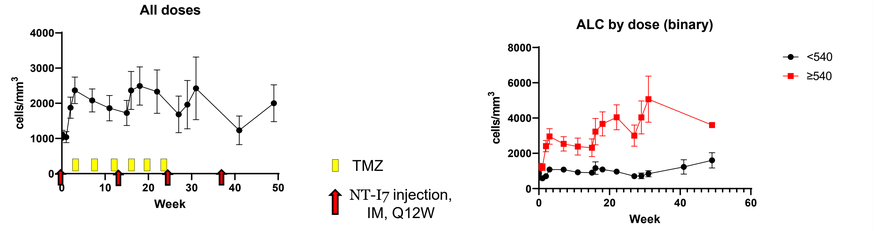


Figure 1. NT-I7 treatment increases peripheral absolute lymphocyte counts (ALC).

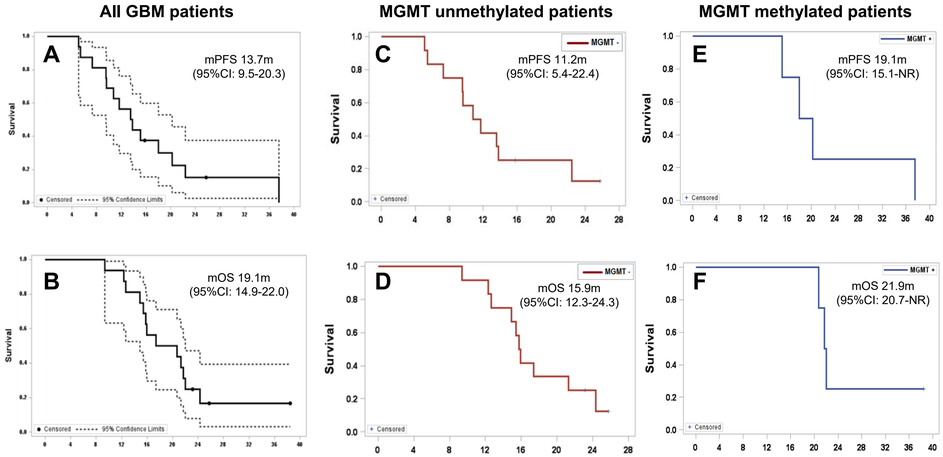


Figure 2. Progression Free Survival (PFS) and Overall Survival (OS) in patients with GBM. A) mPFS in all patients, n=16; B) mOS in all patients, n=16; C) mPFS in MGMT unmethylated patients, n=12; D) mOS in MGMT unmethylated patients, n=12; E) mPFS in MGMT methylated patients, n=4; F) mOS in MGMT methylated patients, n=4. Median follow-up is 25.7 months. Data cut-off as July 15th, 2022.

Conclusions

- NT-I7 is well tolerated in patients with high grade gliomas.
- The maximum tolerated dose (MTD) was determined at 720 µg/kg.
- While elevation of ALC was observed at doses below 540 µg/kg, the increase in ALC was substantially higher at doses 540 µg/kg and above
- Although NT-I7 showed promising PFS and OS, especially in MGMT promoter unmethylated GBM, the clinical benefit of NT-I7 in GBM remains to be determined in future Phase 2/3 clinical trials.
- Phase II and expansion cohort enrollment and 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 2022.

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