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

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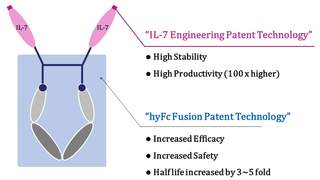
BACKGROUND

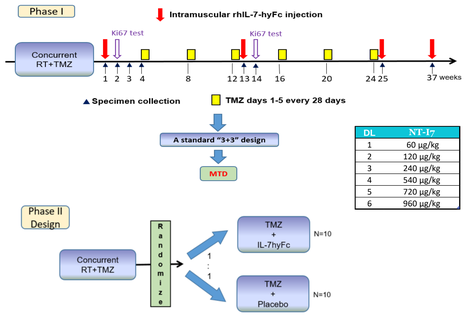
High-grade glioma (HGG) patients can develop prolonged lymphopenia after standard radiation therapy (RT) and temozolomide (TMZ), which has been shown to correlate with worse survival. Levels of Interleukin-7 (IL-7), a cytokine that stimulates T-cell homeostasis and proliferation, is disproportionally low in HGG patients with lymphopenia. NT-I7 (efineptakin alfa) is a first-in-class long-acting recombinant human IL-7 that supports proliferation and survival of CD4+ and CD8+ T-cells in humans and mice. Our previous study demonstrated that NT-I7 could correct lymphopenia and improve the survival of orthotopic murine glioma models. The current study aims to examine the safety of administering NT-I7 after chemoradiotherapy to HGG patients and its effect on systemic absolute lymphocyte counts (ALC).
(Clinical Trial #:NCT03687957).



METHODS

Patients with newly diagnosed HGG who completed concurrent RT/TMZ with ALC≥600 were considered eligible. NT-I7 was administered intramuscularly within 1 week after completion of RT/TMZ and then every 12 weeks for up to 4 doses. Patients also received adjuvant TMZ 4 weeks after RT/TMZ. The phase I study tested 6 dose levels of NT-I7, with an accelerated phase for the first two dose levels followed by the standard 3+3 design. The primary endpoint of this phase I study was the safety of NT-I7 in HGG. The double-blinded randomized Phase II study is ongoing.

Study Schema



DL	NT-I7
1	60 µg/kg
2	120 µg/kg
3	240 µg/kg
4	540 µg/kg
5	720 µg/kg
6	960 µg/kg

RESULTS

Absolute lymphocyte counts (ALC)

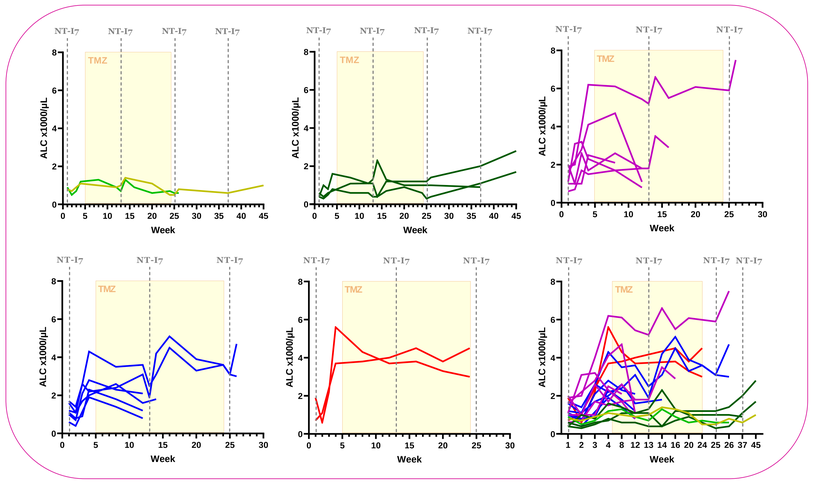
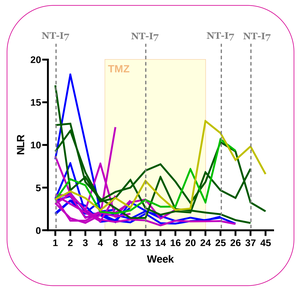


Figure 1. NT-I7 treatment leads to a dose-dependent increase of peripheral ALC counts and a decrease of the NLR.
The biological effect of NT-I7 was significant at DL4 (540 µg/kg), DL5 (720 µg/kg) and DL6 (960 µg/kg).

Neutrophil-to-Lymphocyte ratio (NLR)



Subject characteristics

Table 1. Patients Characteristics

Pt. ID	NT-I7 Dose (µg/kg)	Age	Sex	Diagnosis	MGMT	IDH	Dex (mg/day)	Cycles Received	WBC[1] (cells/mm^3)	Hbg (g/dl)	Plt (K/mm^3)	ANC (cells/mm^3)	ALC (cells/mm^3)	CD4 (cells/mm^3)
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	2	9300	15.1	285	6400	1700	1030
15	720	58	M	GBM	Methylated	WT	0	1	4300	10.4	307	2200	1100	527
16	720	78	F	GBM	Methylated	WT	0	1	6100	13.4	285	5000	600	359
17	720	66	M	GBM	Un-Methylated	WT	4	1	6100	13.7	327	3700	1000	442
18	960	30	M	GBM	Methylated	Mutated	0	1	7300	15.2	251	4400	1900	1045
19	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)

[1]Lab results are from baseline in Week 1

Safety and Tolerability

Table 2. Summary of Treatment-Related Adverse Events

Adverse Event	60 µg/kg n=1 (%)		120 µg/kg n=3 (%)		240 µg/kg n=6 (%)		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
Back pain	0	0	0	0	0	0	0	0	0	0	0	1 (50)*

*** DLTs noted in 960 µg/kg dose level. Thus 720 µg/kg is selected as the phase 2 dose.**

T cell functionality

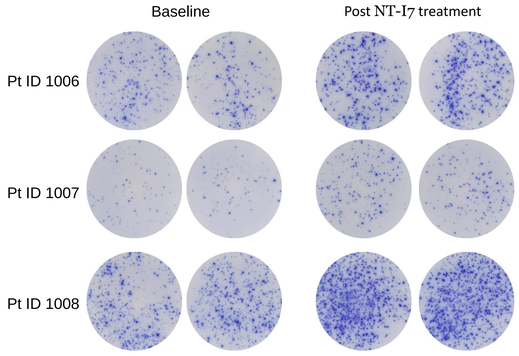


Figure 2. NT-I7 increases the frequency of IFNγ-producing T cells. Representative examples of ex vivo IFNγ production quantified by ELISPOT analysis. Patients were in the 540 µg/kg DL and post-treatment samples correspond to 4 weeks after the first NT-I7 dose.

Clinical response

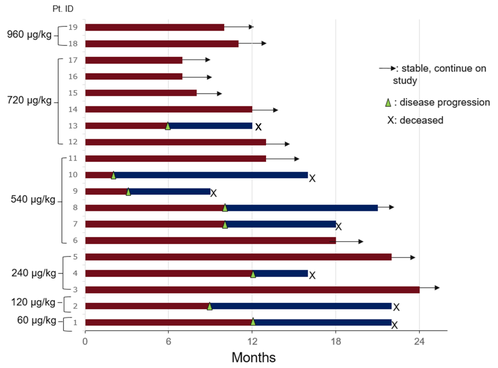


Figure 3. Clinical response. The clinical status of patients (pts) in each dose level are summarized above. Out of 12 MGMT un-methylated GBM patients, 4/12 pts had PFS ≥ 12 months, and 3/12 pts had OS ≥ 18 months at the time of analysis.

CONCLUSIONS

- NT-I7 is well tolerated for HGG patients after chemoradiotherapy and has a RP2D of 720 µg/kg.
- NT-I7 treatment led to dose-dependent significant increases of peripheral ALC as well as increases in IFNγ production.
- NT-I7 treatment let do dose-dependent significant decreases of peripheral NLR.

Immune profiling and cytokine analysis are ongoing and will be updated. The Phase II randomized study to evaluate the effect of NT-I7 vs placebo on ALC and survival is ongoing.

ACKNOWLEDGMENTS

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- Siteman Investment Program provided funding for correlative studies