A Phase 1b Dose Expansion Study Evaluating Safety, Preliminary Anti-Tumor Activity, and Accelerated T Cell Reconstitution with NT-I7 (Efineptakin Alfa), a Long-Acting Human IL-7, Administered Following Tisagenlecleucel in Subjects with Relapsed/Refractory Large B-Cell Lymphoma

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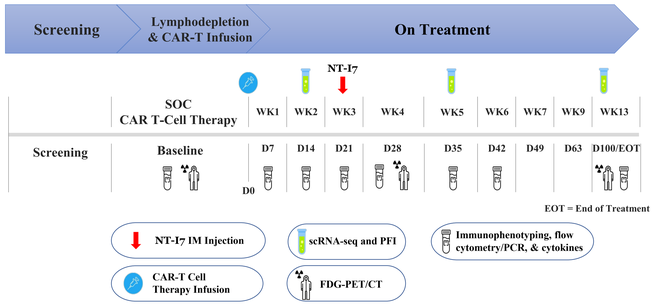
BACKGROUND

Tisagenlecleucel (Kymriah®), a CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy, is standard of care (SOC) for patients (pts) with relapsed/refractory large B-cell lymphoma (r/r LBCL). Successful expansion and persistence of CAR-T cells strongly predicts response to this therapy. NT-I7 (efineptakin alfa) is a first in-class, long-acting human IL-7 that increases the number and functionality of T-cells in peripheral blood and within tumors. We hypothesize that NT-I7 administration after tisagenlecleucel SOC for pts with r/r LBCL may increase expansion and persistence of CAR-T, increasing tumor response rate and improving clinical outcomes without safety concerns.

STUDY DESIGN

This phase 1b study consists of a dose-escalation phase followed by a dose expansion. In dose escalation, subjects receive tisagenlecleucel infusion on Day 0 and a single intramuscular dose of NT-I7 on Day 21, at 7 dose levels (DL1-7): 60, 120, 240, 360, 480, 600, and 720 µg/kg. DL1-2 enrolled 1 subject each, with the remaining DLs following a 3+3 design. Up to 42 subjects will be enrolled for the dose escalation phase. Eligible pts have biopsy-proven diagnosis of r/r LBCL after ≥2 lines of systemic therapy, are eligible for tisagenlecleucel as SOC, and have not yet received prior CD19-directed therapy.



SOC = standard of care, PCR = polymerase chain reaction, FDG-PET/CT = 18F-fluorodeoxyglucose positron emission tomography–computed tomography

Dose Level	DL1	DL2	DL3	DL4	DL5	DL6	DL7
NT-I7, µg/kg	60	120	240	360	480	600	720

STUDY OBJECTIVES

- Primary Objectives: To evaluate safety and tolerability and determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) for NT-I7 with this regimen
- Secondary Objectives: To explore anti-tumor activity and rates of Grade ≥3 Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) after NT-I7 administration post-tisagenlecleucel.
- Exploratory Objectives: To explore the effects of this regimen on expansion of absolute lymphocyte counts (ALC) and expansion of CAR-T cells

CONCLUSIONS

- NT-I7 treatment following tisagenlecleucel SOC was safe and well-tolerated, not inducing CRS or ICANS
- There is a trend for NT-I7 treatment to increase ALC and CAR-T absolute numbers in peripheral blood.
- This study is currently enrolling.

CLINICAL RESULTS

Patient characteristics

- 7 patients were enrolled, with 5 in dose levels (DL) 1-3 (DL1 = 60 µg/kg, DL2 = 120 µg/kg, DL3 = 240 µg/kg).

Table 1. Subject characteristics

Characteristic	Categories	n=7
Age, mean (min, max)		67.1 (55, 80)
ECOG status, n (%)	0	2 (28.6)
	1	5 (71.4)
Stage at diagnosis, n (%)	III	3 (42.9)
	IV	4 (57.1)
Extranodal involvement, n (%)	Yes	4 (57.1)
	No	2 (28.6)
	Unknown	1 (14.3)
Bulky nodal disease, n (%)	Yes	0 (0.0)
	No	6 (85.7)
	Unknown	1 (14.3)
Double or triple hit phenotype, n (%)		0 (0.0)
≥ 2 prior therapies, n (%)		7 (100.0)
Post-autologous stem cell therapy, n (%)		2 (28.6)
CRS after CAR-T infusion, pre-NT-I7, n (%)	Any grade	3 (42.8)
	Grade ≥3	0 (0.0)
ICANS after CAR-T infusion, pre-NT-I7, n (%)	Any grade	1 (14.3)
	Grade ≥3	0 (0.0)

Safety

- All patients in DL1-3 completed the dose-limiting toxicity period.
- Neither CRS nor ICANS were observed following NT-I7 treatment.

Table 2. Summary of adverse events

Event types	Events in DL1 (60 µg/kg, n=1)	Events in DL2 (120 µg/kg, n=1)	Events in DL3 (240 µg/kg , n=3)
TEAE	2	2	9
NT-I7-related TEAE			
Injection site reaction, Gr 1		1	1
Injection site reaction, Gr 2	1		
Vomiting, Gr 1	1		
Immune-related TEAE	2	0	0
TEAE of special interest	2	0	0

TEAE = treatment emergent adverse event

Summary of best overall response

- All patients in DL3 achieved complete response (CR) / complete metabolic response (CMR) as best overall response (BOR), with one disease progression (PD) due to a new lesion at day 90.

Table 3. Summary of best overall response

Dose levels	CR/CMR	PR	SD	PD
DL1, 60 µg/kg (n=1)	-	-	-	1
DL2, 120 µg/kg (n=1)	-	1*	-	-
DL3, 240 µg/kg (n=3)	3**	-	-	-

* Patient progressed at day 90; ** 2 patients CR, 1 patient CMR. 1 CR patient progressed at day 90.
CR = complete response, CMR = complete metabolic response, SD = stable disease, PD = disease progression

BIOMARKER RESULTS

NT-I7 treatment does not induce high levels of inflammatory cytokines

- Strong increases in proinflammatory cytokines such as IL-6 are associated with CRS and ICANS.
- Magnetic bead-based multiplex assay (Luminex®) of plasma samples from DL1-3 patients showed fluctuations in cytokine levels at DL1 (n=1). However, patients at higher dose levels showed inflammatory cytokine levels that were stable or did not rise to the level of concern for CRS and ICANS.

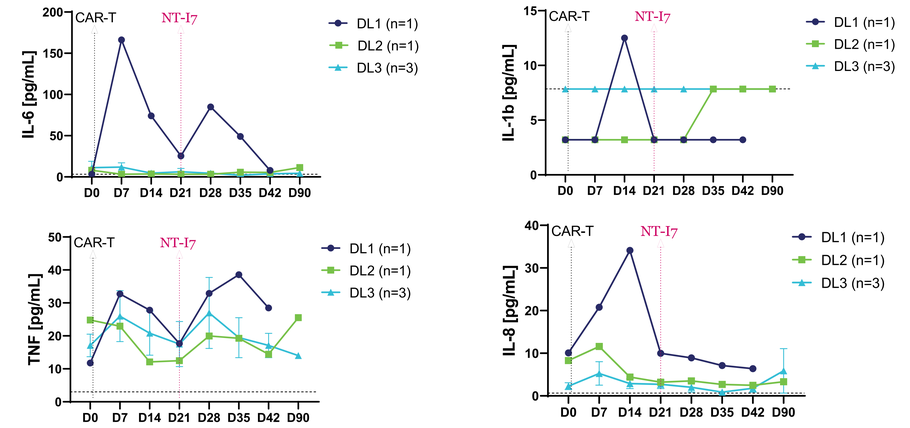


Figure 1. Proinflammatory cytokines associated with CRS and ICANS were mostly stable or did not increase to levels of concern following NT-I7 administration. DL1 = 60 µg/kg, n=1; DL2 = 120 µg/kg, n=1; DL3 = 240 µg/kg, n=3. Mean ± SEM.

NT-I7 increases absolute numbers of lymphocytes and CD19 CAR-T cells

- A single dose of NT-I7 significantly increased peripheral absolute lymphocyte counts (ALC), especially at DL3 (Figure 2).
- A single dose of NT-I7 at the CAR-T contraction phase increased absolute numbers of CD19 CAR-T cells (Figure 3).
- Despite the limited number of patients enrolled in the lowest NT-I7 dose levels, and CAR-T levels being near the limit of assay detection, this increase in CAR-T is promising and may have strong clinical implications.

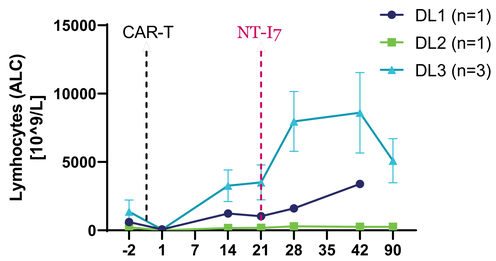


Figure 2. ALC kinetics after tisagenlecleucel (Day 0) and NT-I7 (Day 21) administration in each dose level. DL1 = 60 µg/kg, n=1; DL2 = 120 µg/kg, n=1; DL3 = 240 µg/kg, n=3. Mean ± SEM.

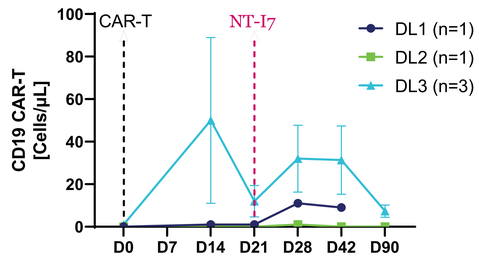


Figure 3. CD19 CAR-T PK, measured by flow cytometry, after tisagenlecleucel (Day 0) and NT-I7 (Day 21) administration in each dose level. DL1 = 60 µg/kg, n=1; DL2 = 120 µg/kg, n=1; DL3 = 240 µg/kg, n=3. Mean ± SEM.

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