



A Phase 1b Study Evaluating the Safety, Tolerability and Preliminary Anti-tumor Activity of NT-I7 (efineptakin alfa) a Long-acting Human IL-7, post- Kymriah[®] (Tisagenlecleucel), post-Yescarta[®] (Axicabtagene ciloleucel), or post-Breyanzi[®] (Lisocabtagene Maraleucel) in Subjects with Relapsed/Refractory Large B-cell Lymphoma

Protocol Number: NIT-112

Version: v11.0 (incorporating Amendment 10)

Products: NT-I7 (efineptakin alfa)
Kymriah[®] (Tisagenlecleucel)
Yescarta[®] (Axicabtagene ciloleucel)
Breyanzi[®] (Lisocabtagene Maraleucel)

Abbreviated Title: Relapsed/Refractory Large B-cell Lymphoma with NT-I7 post-CD19 CAR T-cell Therapy

Study Phase: Phase 1b

IND Number: 148163

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Title



Sponsor (signature)

20 Nov 2023

Date

1.0 SIGNATURE OF INVESTIGATOR

Protocol Title:

A Phase 1b Study Evaluating the Safety, Tolerability
and Preliminary Anti-tumor Activity of NT-I7
(efineptakin alfa) a Long-acting Human IL-7, post-
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(Lisocabtagene Maraleucel) in Subjects with
Relapsed/Refractory Large B-cell Lymphoma

Protocol Number: NIT-112

Version: v11.0, dated 20-NOV-2023

This protocol is a confidential communication of NeoImmuneTech. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy by e-mail to xxx@neoimmunetech.com

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

Revisions to Protocol Version 11.0

Section #	Section Title	Change	Justification
Throughout	All	Updated protocol date and version number	
3.0 7.1.1 7.8	Protocol Synopsis Dose Escalation Phase Rationale for Staggered Dosing and 3-week DLT Period	Revised to indicate that, instead of simultaneous enrollment after DL5 in the dose escalation phase, if the first subject does not experience dose limiting toxicity in the first 2 weeks, the second and third subjects can be dosed simultaneously.	No dose limiting toxicities occurred through DL5, and no subjects experienced adverse drug reactions for the first time between 14 and 21 days.
		Removed reference to simultaneous enrollment after the first subject clears the 3-week DLT period at DL4 and onward.	Simultaneous enrollment was never implemented.
6.1	Inclusion Criteria	Replaced text in Criterion 9g, "Creatinine $\leq 1.5 \times \text{ULN}$ or Creatinine clearance (CrCl) $\geq 30 \text{ mL/min}$ for subject with creatinine levels $> 1.5 \times \text{ULN}$ as determined by Cockcroft-Gault (using actual body weight or 24-hour urine creatinine clearance", with "Creatinine clearance (CrCl) $\geq 30 \text{ mL/min}$ as calculated per institutional standard."	To provide more accurate standard for evaluating renal function.

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3.0 PROTOCOL SYNOPSIS

Title	A Phase 1b Study Evaluating the Safety, Tolerability and Preliminary Anti-tumor Activity of NT-I7 (efineptakin alfa) a Long-acting Human IL-7, post-Kymriah [®] (Tisagenlecleucel), post-Yescarta [®] (Axicabtagene ciloleucel), or post-Breyanzi [®] (Lisocabtagene Maraleucel) in Subjects with Relapsed/Refractory Large B-cell Lymphoma
Hypothesis	We hypothesize that the administration of NT-I7 following standard of care (SOC) approved CD19 CAR T-cell therapies for subjects with r/r LBCL will be safe, tolerable and may increase the expansion and persistence of CAR T-cells in-vivo, which may result in increased tumor response rate and improved clinical outcomes.
Study Phase	Phase 1b
Study Type	A multicenter Phase 1b study evaluating the safety, tolerability and preliminary anti-tumor activity of NT-I7 administration following SOC CAR T-cell therapy
Primary Objectives	<u>For Dose Escalation Phase:</u> ○ To evaluate the safety and tolerability of NT-I7 when administered after SOC CAR T-cell Therapy infusion for r/r LBCL ○ To determine the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D) of NT-I7 when administered after SOC CAR T-cell Therapy infusion for r/r LBCL ○
Secondary Objectives	<u>For Dose Escalation phase:</u> ○ To explore the preliminary anti-tumor activity of NT-I7 when administered after CAR T-cell Therapy infusion for r/r LBCL based on: ▪ Duration of Response (DOR) ▪ Progression-Free Survival (PFS) ▪ Overall Survival (OS) <u>For Dose Escalation and Dose Expansion phases:</u> ○ To continue evaluating the effect of NT-I7 when administered after CAR T-cell Therapy infusion on safety profile with regards to: ▪ Rates of grade 3 and higher Cytokine Release Syndrome (CRS) ▪ Rates of grade 3 and higher Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) ○ The effect of NT-I7 on CAR-T cells expansion
Exploratory Objectives	<u>For Dose Escalation and Dose Expansion phases:</u> ○ To make a preliminary assessment of PK parameters of CAR T-cell Therapy when administered NT-I7 post-SOC CAR T-cell therapy

	▪ Parameters of expansion, including maximum concentration (C_{max}) and time to maximum concentration (T_{max}) ▪ Parameters of persistence, including the terminal half-life ($T_{1/2}$), last measured concentration (C_{last}), and time of last measured concentration (T_{last}) Area under the curve for CAR T-cell expansion for days 0-21 (prior to NT-I7 administration), and days 22-100 (after NT-I7 administration and 3 months post CAR T-cell Therapy infusion) ○ To evaluate the immunogenicity of NT-I7 ▪ Incidence of anti-drug antibody (ADA) to NT-I7 during the study relative to Day 21 (pre-dose NT-I7) ○ To evaluate the Pharmacokinetic profile of NT-I7 ▪ Serum concentration of NT-I7 administered on Day 21 pre-dose and at specified timepoints for the following parameters: Area under the concentration time-curve (AUC), maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), and clearance (CL). <u>For the Dose Expansion phase:</u> To explore the Overall Response Rate (ORR) of NT-I7 when administered after SOC CAR T-cell Therapy infusion for r/r LBCL
Correlative Studies	For Dose Escalation and Dose Expansion phases: ○ To evaluate the effect of NT-I7 when administered after SOC CAR T-cell Therapy on the expansion of lymphocytes, CAR T-cells, and serum cytokines in vivo by: ▪ Flow cytometry-based comprehensive immunophenotyping of T cells, T-cell subtypes and myeloid subsets in peripheral blood. Additional markers may include, but are not limited to, Ki-67 ▪ Quantitative DNA PCR and/or FACS for measuring CAR T-cell expansion ▪ Plasma cytokine profiling ▪ Single cell RNA sequencing (scRNA-seq) of peripheral blood before NT-I7 administration, on D35 +/- 2 days (i.e., approximately 2 weeks after NT-I7 administration), and at the time of relapse ▪ LBCL immunophenotyping pre-treatment (before CAR T-cell Therapy infusion) and at the time of relapse ▪ Polyfunctional analyses to assess the number and percentage of CAR T-cell and non-transduced T cells that are able to express and secrete various cytokines and chemokines before NT-I7 administration and on D35 +/- 2 days

	<u>For Dose Expansion phase:</u> ○ To correlate baseline and post-treatment responses ▪ Plasma minimum residual disease (MRD) and compared to SOC FDG PET-CT imaging
Study Design	This is a multicenter Phase 1b study evaluating the safety, tolerability and preliminary anti-tumor activity of NT-17 administration following SOC CAR T-cell therapy for eligible subjects with r/r LBCL. The study consists of a Dose Escalation phase followed by a Dose Expansion phase. Dose Escalation phase The Dose Escalation phase is designed to assess the safety and tolerability, including determination of the MTD and/or the RP2D, of NT-17 when administered after CAR T-cell Therapy infusion for r/r LBCL. Seven dose levels (DLs) are planned: the starting DL (DL1) will be 60 µg/kg, and the highest DL to be tested (DL7) will be 720 µg/kg, as outlined in the Treatment Schema. Other intermediate DLs between 60 µg/kg and 720 µg/kg may be explored based on emerging data. The Dose Escalation phase will begin with an accelerated phase with 1 subject per cohort at the first 2 DLs (DL1 = 60 µg/kg and DL2 = 120 µg/kg), followed by a standard 3+3 design on the remaining 5 DLs (see Treatment Schema), each with a cohort of 3 independent subjects each time and with a maximum total of 6 subjects per cohort. If at least 2 Grade ≥ 2 AEs or any 1 Dose Limiting Toxicity (DLT) are observed in the single subject enrolled in either DL1 or DL2, the accelerated phase will convert to a conventional 3+3 design at the DL where the AEs or DLT are observed and remain so for all the DLs above. In addition to converting to the 3+3 design, the next DL will not exceed 50% of the previous DL. Similarly, if a 2nd DLT occurs in a DL, the next DL in the escalation scheme will not exceed 33% of the previous DL. In all DLs that followed the 3+3 design in DL1-5, subjects were dosed in a 3-week staggered fashion: the 1st subject in a DL was monitored for 3 weeks; after 3 weeks, if the safety was acceptable, the 2nd subject was enrolled and treated at that same DL; similarly, the 3rd subject was enrolled and treated only if the safety appeared to be acceptable for both the 1st and 2nd subjects after the 2nd subject has been monitored for 3 weeks. If additional subjects were required for a DL, they would be enrolled and treated in similar 3-week staggered fashion. No DLTs were observed in Dose Levels 1-5. There was no subject at any dose level who experienced the first ADR between 14 days to 21 days after NT-17 administration. Given these results, starting at Dose Level 6, if a DLT is not observed in the first subject after 2 weeks, then the second and third subjects can be dosed simultaneously. The DSMC will occur once the final subject in a cohort has completed the 3-week DLT period.

Dose Expansion phase

Once RP2D has been determined from the Dose Escalation phase, up to 15 subjects will be enrolled in the Dose Expansion phase and treated at the RP2D to further evaluate the safety and preliminary anti-tumor activity of NT-I7 administration following SOC CAR T-cell therapy for eligible subjects with r/r LBCL. Subjects in the Dose Expansion cohort can enroll simultaneously.

Study Stopping Rules (applicable to both Dose Escalation and Dose Expansion phases): refer to [Section 7.3](#) for details.

Treatment Plan:

- **NT-I7 (aka rhIL-7-hyFc, efineptakin alfa):**
NT-I7 will be administered as an intramuscular (IM) injection at the appropriate DL for each cohort. Each subject will receive only one NT-I7 injection administered on Day 21 +/-2 days (post-CAR T-cell Therapy infusion). Subjects will be hospitalized for NT-I7 injection and monitored for at least 24 hours after NT-I7 injection. If subjects develop Grade 2 or higher AEs, subjects will remain hospitalized until resolution of AEs to grade 1 or better. Subjects can be kept in the hospital longer at the discretion of the treating physicians.
- **Kymriah®:**
Kymriah will be administered per manufacturer's recommendations and in accordance with FDA prescribing guidelines and best institutional practices for SOC use.
- **Yescarta®:**
Yescarta will be administered per manufacturer's recommendations and in accordance with FDA prescribing guidelines and best institutional practices for SOC use.
- **Breyanzi®:**
Breyanzi will be administered per manufacturer's recommendations and in accordance with FDA prescribing guidelines and best institutional practices for SOC use.
- **Duration of Treatment, Study and Follow-up:**
The enrollment date is at the start of NT-I7 treatment. The duration on study will be approximately 3 months following NT-I7. Subjects will then be followed up per standard of care and per the REMS program for the SOC CAR T-cell therapy the subject received.

Guideline for Managing Cytokine Release Syndrome (CRS):

Subjects will be closely monitored for the development of fever, hypotension and hypoxia. Treatments including the use of tocilizumab and corticosteroids will be implemented, as appropriate, following the modified version of American Society for Transplantation and Cellular Therapies (ASTCT) grading guideline. Refer to [Section 10](#) for details.

	<u>Guideline for Managing Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS):</u> Subjects will be closely monitored with frequent neurologic examinations. Immune effector cell-associated neurotoxicity syndrome (ICANS) will be graded using ASTCT guideline and managed by using, tocilizumab, siltuximab, and as appropriate Refer to Section 10 for details. <u>Disease Assessments:</u> Prior studies evaluating recombinant human IL-7 have reported spleen and lymph nodes increased both in size and FDG uptake following rhIL-7 administration, and remained elevated above baseline for 8 weeks (1). Additionally, recent data have demonstrated improved specificity and similar sensitivity of Immunoglobulin High-Throughput Sequencing (Ig-HTS) of plasma (cell-free DNA) for minimal residual disease (MRD) surveillance compared to SOC FDG PET-CT in DLBCL (2). Therefore, in order to effectively monitor early disease response following CAR T-cell Therapy and NT-I7 treatment, subjects will be assessed at baseline, D28 and D100 with FDG PET-CT and at baseline, D7, D21, D28, and D100 with plasma MRD (2). Tumor assessment with FDG PET-CT or CT as SOC will be performed at 6 months and 12 months post-CAR T-cell Therapy during survival follow-up. The results of FDG PET-CT and CT scans will be reviewed and assessed by the Investigators using the Lugano classification (3).																
Treatment Schema	Dose Escalation¹ <table> <tr> <th>Dose Level (DL)²</th><th>NT-I7 Dose</th></tr> <tr><td>1</td><td>60 µg/kg</td></tr> <tr><td>2</td><td>120 µg/kg</td></tr> <tr><td>3</td><td>240 µg/kg</td></tr> <tr><td>4</td><td>360 µg/kg</td></tr> <tr><td>5</td><td>480 µg/kg</td></tr> <tr><td>6</td><td>600 µg/kg</td></tr> <tr><td>7</td><td>720 µg/kg</td></tr> </table> Dose Expansion ¹ DL 1-2: accelerated escalation (1 subject/DL); DL 3-7: 3+3 design ² Intermediate DLs between 60 µg/kg and 720 µg/kg may be explored based on emerging data	Dose Level (DL) ²	NT-I7 Dose	1	60 µg/kg	2	120 µg/kg	3	240 µg/kg	4	360 µg/kg	5	480 µg/kg	6	600 µg/kg	7	720 µg/kg
Dose Level (DL) ²	NT-I7 Dose																
1	60 µg/kg																
2	120 µg/kg																
3	240 µg/kg																
4	360 µg/kg																
5	480 µg/kg																
6	600 µg/kg																
7	720 µg/kg																

	The diagram illustrates the study timeline across three main phases: Screening, Lymphodepletion & CAR-T Infusion, and On Treatment. Key events include SOC CAR T-Cell Therapy at Baseline, NT-17 IM Injection at D0, and various blood draws and scans (MRD, FDG-PET/CT) through Week 15. EOT is marked at D100.
Primary Endpoints and Statistical Considerations	Endpoints/Statistical Considerations: <u>Primary Endpoint:</u> The primary endpoint will be the safety and tolerability, including determination of the MTD and/or the RP2D, of NT-17 when administered after SOC CAR T-cell Therapy in subjects with r/r LBCL, as assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, except grading of CRS and ICANS which will be based on ASTCT guidelines. - The MTD will be defined as the dose of NT-17 that yields a DLT rate $\leq 33\%$. If an MTD is not reached, the highest administered dose evaluated for safety will be 720 $\mu\text{g/kg}$. - The DLT period and definition: - DLT period: from NT-17 administration until 21 days after - DLT definition: Dose-limiting toxicity is defined as any AE occurring within the first 21 days after NT-17 injection that is considered to be at least possibly, probably, or definitely related to the study treatment (NT-17) per the investigator, and that meets at least one of the non-hematologic or hematologic criteria listed below. <u>Hematologic criteria</u> - Any Grade 5 toxicity - Grade 4 neutropenia lasting more than 5 days - Febrile neutropenia of more than 5 days ($\text{ANC} < 1.0 \times 10^9/\text{L}$, fever $\geq 38.5^\circ\text{C}$) - Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding or - any requirement for platelet transfusion not recovering to baseline at the end of DLT period - Grade 4 anemia, unexplained by underlying disease

	▪ Grade 4 hematological toxicities lasting more than 21 days <u>Non-hematologic criteria</u> ▪ Any Grade 5 toxicity ▪ Grade 3 or higher non-hematologic toxicity. ▪ Hy's law criteria ▪ Any Grade ≥ 4 CRS or Grade 3 CRS that does not improve to Grade ≤ 1 within 72 hours ▪ Any Grade ≥ 3 ICANS. Note: Grading of CRS and ICANS is based on ASTCT guidelines The following exceptions are acceptable (i.e., not considered as DLTs). ▪ Grade 3 or 4 electrolyte abnormalities that lasts < 24 hours to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions ▪ Grade 3 nausea, vomiting or diarrhea that resolves to Grade 2 or less within 72 hours with symptomatic treatment ▪ Grade 3 liver enzyme abnormalities improving to grade 2 or better within 72 hours ○ Determination of the RP2D: the RP2D will be based on an accumulation of all available data. All available data including clinical PK, PD, anti-tumor activity (including best ORR) and safety, and nonclinical pharmacology data will be pooled. Integrated dose-response and exposure-response analyses will be conducted to determine the RP2D. • <u>Sample Size and Justifications:</u> Dose Escalation phase: 17-42 subjects. Dose Expansion phase: 15 subjects are planned for enrollment to ensure 13 evaluable subjects.
Eligibility Criteria	<u>Inclusion Criteria:</u> ○ Able to provide written informed consent (or consent from a legally authorized person) ○ ≥ 18 years of age at the time of signing informed consent

	○ Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 ○ Must be eligible for treatment with an FDA approved SOC CD19 CAR T-cell Therapy respective to the current FDA approved CAR-T label for Yescarta, Breyanzi, or Kymriah. ○ Subjects with histologically confirmed relapsed or refractory LBCL ○ Subjects must have measurable disease by IWG response criteria for lymphoma. Subjects that received bridging therapy pre-lymphodepletion will be allowed for enrollment regardless of re-staging results (PMR or CMR), even if the lesion is not measurable by the criteria mentioned above. ○ Subjects must have life expectancy greater than or equal to 12 weeks ○ Adequate organ function per institutional guidelines at the start of lymphodepleting chemotherapy as pre-conditioning for CAR T-cell infusion ○ Negative pregnancy test (women of child-bearing age) and willing to use effective contraception (all subjects) ○ ECG demonstrating Fridericia's corrected QT interval (QTcF) < 500 ms. Patients with QTcF ≥ 500 ms will require clearance by a local cardiologist.
	○ Exclusion Criteria: ○ In Dose Escalation phase: Grade ≥3 CRS or ICANS post-CAR T-cell infusion. Note: Grade 1 CRS or ICANS must be completely resolved at least 3 days prior to NT-I7 injection ○ In Dose Expansion phase: Grade ≥3 CRS or ICANS post-CAR T-cell infusion. Note: Grade 1 or 2 CRS or ICANS must be completely resolved >3 days prior to NT-I7 injection ○ Pregnant or breastfeeding ○ Concurrent chemotherapy or biologic or hormonal therapy for cancer treatment ○ Had previously received an allogeneic tissue/solid organ transplant or bone marrow transplant ○ Has active central nervous involvement of LBCL ○ Has active autoimmune diseases including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barre syndrome, multiple sclerosis, vasculitis or glomerulonephritis

	○ Has active and clinically relevant bacterial, fungal, viral, or TB infection, including known Hepatitis A, B, or C or HIV (testing not required) ○ Concurrent enrollment in another clinical study unless it is noninterventional. ○ Receipt of any conventional or investigational anticancer therapy not otherwise specified in the eligibility criteria within 30 days prior to NT-I7 injection. ○ Unresolved toxicities from prior anticancer therapy. ○ Receipt of live, attenuated vaccine within 30 days prior to NT-I7 injection. ○ For whom intramuscular therapy is contraindicated ○ Has clinically significant cardiac disease.
Number of Subjects	Up to 57 subjects are planned to be enrolled (up to 42 subjects in the Dose Escalation phase and up to 15 subjects in Dose Expansion phase).
Number of Clinical Sites	Approximately 20 study sites are planned to participate in this study.
Duration of Participation	Each subject will participate in the study from the time the Informed Consent Form (ICF) is signed through final protocol-specific follow-up. The active study will end when the last subject completes the Day 100 End of Treatment visit.
Estimated Treatment Duration of Study	Approximately 3 months
Estimated Duration of Study	Approximately 24 months after last subject enrolled

4.0 INTRODUCTION

4.1 Disease Background

4.1.1 Diffuse large B-Cell Lymphoma (DLBCL) and Treatment of DLBCL

Diffuse large B-cell lymphoma is the most commonly occurring subtype of non-Hodgkin lymphoma (NHL), accounting for 25% to 30% of all NHL and >20,000 cases in the U.S annually (4). Despite improvement in therapeutic options, treatment is often not curative with as many as 50% of patients with adverse risk factors developing r/r disease (5). Prior to the availability of CAR-T therapy, prognosis for patients with r/r DLBCL was very poor with objective response (OR) rates and complete response (CR) rates to salvage chemotherapy of 26% and 7% respectively, and median overall survival (OS) of 6.3 months (6).

This subtype of cancer is heterogeneous and aggressive, yet scientific advances in the last quarter century have rendered it curable with chemotherapy or with combined chemotherapy and immunotherapy. Until 1998, the standard regimen for DLBCL treatment included cyclophosphamide, vincristine, doxorubicin, and prednisone, referred to as “CHOP” (7). The standard of care in the United States, Europe, and other high-income settings now includes a combination of the four chemotherapy drugs plus immunotherapy with the humanized monoclonal antibody directed at CD20, rituximab (RCHOP) (7). The addition of the anti-CD20 monoclonal antibody rituximab (R) to the standard CHOP regimen was a major breakthrough in the frontline treatment for patients with DLBCL, resulting in dramatic improvements in PFS and OS (8-10). However, despite these improvements approximately 40% of patients with DLBCL who are treated with R-CHOP or R-CHOP-like chemotherapy will relapse or develop refractory disease (11, 12), and the majority of patients with r/r DLBCL will succumb to the disease.

Chimeric antigen receptor (CAR) T-cell therapy is a new method of cancer treatment whereby autologous T cells are genetically engineered ex vivo and then reinfused into the patient (13). The CAR portion of the T cell contains proteins that allow the T cells to recognize and induce a targeted immune response against specific cancer cells that express the corresponding antigen. This specificity enables CARs to be independent from HLA-peptide complexes, in contrast to transduced T cell receptors (TCRs), which require peptide processing or HLA expression to be recognized (14). To date, CD19 is the main target of CAR T-cells as it is broadly expressed on B-cell cancers and has limited expression on normal B cells (13).

CAR T-cell therapy has revolutionized modern cancer therapy, with 3 anti-CD19 CAR T-cell therapies receiving FDA approval for r/r B-cell lymphoma/leukemia, and many other CAR T-cell therapies for solid and liquid tumors currently undergoing testing in clinical studies. Tisagenlecleucel (CTL019, hereafter referred to as Kymriah), axicabtagene ciloleucel (KTE-C19, hereafter referred to as Yescarta™) and lisocabtagene maraleucel (hereafter referred to as Breyanzi) are available for third or later-line treatment of r/r LBCL (15) (16).

All three CAR-T therapies share a core CAR structure, an extracellular anti-CD19 binding domain derived from the murine FMC63 antibody, a transmembrane region, an intracellular co-stimulatory domain (either CD28 or 41BB) and the intracellular T-cell receptor signaling domain. CAR T-cells

with either a CD28 (Yescarta) or 4-1BB (Kymriah and Breyanzi) co-stimulatory domain are effective for the treatment of patients with r/r LBCL (17-19).

4.1.2 Tisagenlecleucel (Kymriah®)

Clinical benefit of Kymriah® in DLBCL has been reported in the JULIET study. The JULIET study (NCT02445248) was an open-label, multicenter, single-arm trial in patients ≥ 18 years of age with relapsed or refractory DLBCL, who received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT). According to the most recent labeling information (19), out of the efficacy evaluable population of 68 patients, the best ORR was 50% (95% confidence interval [CI]: 37.6% to 62.4%), with 32% CR. The results of this study led to FDA approval of Kymriah for patients with r/r LBCL including DLBCL, not otherwise specified (NOS), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma after having received 2 or more lines of systemic therapy.

4.1.3 Yescarta®

Clinical benefit of Yescarta® in B-cell lymphomas has been reported in the ZUMA studies. The ZUMA-1 trial (NCT02348216) was a single-arm, multicenter, phase 1-2 trial. Eligible patients were adults with relapsed or progressed histologically confirmed large B-cell lymphoma, including diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma. According to the most recent labeling information (18), out of 101 Yescarta recipients, 73 patients (72%) achieved objective response (95% CI: 62, 81), with 52 patients (51%) achieving CR (95% CI: 41, 62). The follow-up study ZUMA-7 (NCT03391466) is a randomized (1:1), international, phase 3 trial for patients with large B-cell lymphoma refractory or relapsed (less than 12 months) to first-line chemo-immunotherapy. Patients were randomized to receive either Yescarta or standard of care. Best objective response rate for 180 patients randomized to receive Yescarta was 83% (95% CI: 77, 88), compared to 50% (95% CI: 43, 58) in the standard therapy arm. The primary efficacy measurement for this study was event-free survival (EFS). At 18 months, estimated EFS rate was 41.5% (95% CI: 34.2, 48.6) in the Yescarta arm compared to 17.0% (95% CI: 11.8, 23.0) for the standard therapy arm. Thus, the primary endpoint analysis showed that Yescarta was superior to the standard of care in these patients. The results led to FDA approval of Yescarta for the treatment of:

- Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.(18)
- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.(18)

4.1.4 Breyanzi®

Clinical benefit of Breyanzi in adult patients with r/r LBCL after at least 2 lines of therapy was reported in the TRANSCEND study. (20) TRANSCEND NHL 001 (NCT02631044) was a

multicenter seamless study conducted in 14 cancer centers in the USA. Eligible subgroups included DLBCL, double-hit and triple-hit DLBCL, DLBCL transformed from any indolent lymphoma, primary mediastinal BCL and follicular lymphoma grade 3B. Per the most recent labeling information for Breyanzi (17), out of 192 patients in the main efficacy set, 73% achieved objective response (141 CRs + PRs, 95% CI 67-80). 104 patients achieved CR (54%, 95% CI 47-61). 287 patients underwent leukapheresis and had radiographically evaluable disease – in this group, 27 additional patients achieved a response. ORR was 59% (95% CI 53-64) with a CR rate of 43% (95% CI 37-49).

Clinical benefit of Breyanzi was reported for adult patients with r/r LBCL after first-line chemoimmunotherapy in the TRANSFORM study (NCT03575351) (17). Eligible patients had not received treatment for r/r lymphoma, were potential candidates for autologous HSCT, and had primary refractory disease or relapse within 12 months of CR to chemoimmunotherapy. 184 pts were randomized to receive either a single infusion of Breyanzi or standard therapy. 89 of the 92 patients randomized to Breyanzi received Breyanzi. EFS was the primary efficacy measure, and the estimated 1-year EFS was 45% (95% CI: 29, 59) in the Breyanzi arm compared to 24% (95% CI: 14, 35) in the standard therapy arm. Estimated median DOR was not reached (NR) for the 92 patients in the Breyanzi arm in patients who achieved CR (95% CI: 7.9 months, NR) (N=61), and was 2.3 months (95% CI: 2.1, NR) in patients with a best response of PR (N=18).

Clinical benefit was reported for transplant-ineligible patients with r/r LBCL after one line of chemoimmunotherapy (17). Patients in the single-arm, open-label, multicenter PILOT study (NCT03483103) were not eligible for high-dose therapy and autologous hematopoietic stem cell transplantation (HSCT). 61 of the 74 patients who underwent leukapheresis received Breyanzi, and efficacy was evaluated based on CR rate and DOR. 33 patients (54%, 95% CI: 41, 67) in the Breyanzi-receiving group achieved CR, compared to 34 (46%, 95% CI: 34, 58) out of the total group of leukapheresed patients. mDOR for patients with a best response of CR was not reached (NR) (95% CI: 11.2, NR), and 2.1 months (95% CO: 1.4, 2.3) for patients with a best response of PR.

In all patients receiving Breyanzi for LBCL, 46% of patients had CRS of any grade, with 3.1% of patients having grade 3 or higher, and 33% had neurologic toxicities of any grade, with 10% at grade 3 or higher.

The FDA has approved Breyanzi for the treatment of LBCL, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:

- Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
- Refractory disease to first-line chemoimmunotherapy or relapse after first line chemoimmunotherapy and are not eligible for HSCT due to comorbidities or age; or
- Relapsed or refractory disease after two or more lines of systemic therapy.

However, as a limitation of use, Breyanzi is not indicated for the treatment of patients with primary central nervous system lymphoma.

4.1.5 CAR T-cell Expansion Is a Strong Predictor of Response to CAR T-cell Therapy

Further analysis of the studies evaluating CD19 CAR T-cell therapies has revealed that the degree of in vivo CAR T-cell expansion by peak concentration (2- to 4-fold higher) and area under the curve (AUC) (4- to 8-fold higher) in the first 28 days following Yescarta® infusion plays a key role in predicting response to therapy, with greater expansion correlating with improved response rates and longer durations of response. In the ZUMA-1 study with Yescarta, CAR T-cells peaked within 14 days of the infusion and were still detectable in a majority of patients by Day 180. CAR T-cell levels by Day 28 (AUC₀₋₂₈) were 5.4 times higher in patients with CR versus non-responders ($p < 0.001$) (21). In the TRANSCEND study with Breyanzi, higher concentrations and AUC₀₋₂₈ levels of CAR T-cell expansion were also associated with clinical and durable responses (22). These data suggest that strategies to increase early CAR T-cell expansion in vivo may translate into a greater proportion of patients achieving an OR, as well as a greater proportion of patients achieving a CR.

4.2. Interleukin-7 (IL-7) and NT-17 Background

4.2.1 Interleukin-7 (IL-7) and T-cell Function

IL-7, which is constitutively produced by stromal cells of the bone marrow and thymus, plays a crucial role in T-cell homeostasis by inducing thymic differentiation, peripheral expansion, and extrathymic differentiation (23, 24). IL-7 is the main regulator of T-cell homeostasis, inducing T-cell growth and proliferation in lymphopenic patients (25). Regulatory T cells (T-regs) have a very low level of IL-7 receptor expression and recent studies suggest that IL-7 therapy does not expand regulatory T cells (1, 26). Meanwhile, IL-7 can induce rapid expansion of other T-cell populations while also preventing exhaustion of effector T cells (27-29). Upon stimulation with IL-7, exhausted T cells also demonstrated increased phospho-STAT5 expression compared to controls (30). These findings suggest that exposure of T cells to IL-7 may expand T-cells, prevent T-cell exhaustion, and improve effector functions, while not expanding regulatory T cells.

4.2.2 Recombinant Human IL-7 (rhIL-7)

rhIL-7 has been administered to healthy volunteers and patients with multiple solid tumors with good tolerance and limited toxicity. In one early human study, patients with refractory cancers received rhIL-7 every other day for 14 days (total 8 doses). CD3⁺ counts dropped in the first 3 days due to trafficking of T cells out of peripheral circulation and into lymphatic tissue, then increased back to baseline by Day 7, and peaked on Day 14, with 200% to 300% increases in lymphocyte counts that remained elevated for up to 6 weeks (31). IL-7 receptor expression on these T cells first downregulated, then returned to baseline by Day 21 (31). Observed Ki-67 expression, a proliferative marker, peaked at 7 days, and returned back to baseline by Day 14. Spleen and lymph nodes increased both in size and fluorodeoxyglucose (FDG) uptake and remained elevated for 8 weeks after infusion, with a peak 14 days after infusion (31). Over 400 patients have received rhIL-7 in multiple clinical studies for a variety of disorders, including the human immunodeficiency virus (HIV), idiopathic lymphopenia, cancer, hepatitis C, sepsis, and bone marrow reconstitution following hematopoietic stem cell transplantation (6, 32). rhIL-7 has been well tolerated, and the drug has mainly been administered in the outpatient setting. The most common AEs observed have been low-grade fever, malaise, transient increases in liver enzyme levels, and erythema and induration at the site of administration (32). Despite producing massive expansion of T cells, IL-7

stimulation rarely induces hyperinflammation or manifestations of acute cytokine storm (27). Importantly, there have been no reports of rhIL-7 causing CRS, a serious immune-mediated adverse reaction caused by excessive immune activation associated with CAR-T therapies and other immune therapeutics [refer to the Investigators' Brochure].

Although these combined clinical studies have demonstrated proof of mechanism in humans with regards to the safety, tolerability, and substantial increases in T-cell count, rhIL-7 as a therapeutic previously faced numerous technical challenges including a short half-life of the drug, a lack of molecular stability of the intrinsically unstable protein, and the consequent poor production yield.

4.2.3. NT-I7 (aka rhIL-7-hyFc, efineptakin alfa)

NT-I7 is a long-acting human IL-7 cytokine, consisting of an rhIL-7 fused to a hybrid Fc region of a human antibody (hyFc), which extends the half-life of NT-I7. In nonclinical studies, NT-I7 increased peripheral T cells, antitumor efficacy, and tumor infiltrating lymphocytes, either as a monotherapy or in combination with chemo/radiotherapy and/or immune checkpoint inhibitors, and CAR-T therapy. In clinical studies, NT-I7 has demonstrated a well-tolerated safety profile and administration of NT-I7 led to a dose-dependent increase in the peripheral CD4⁺ and CD8⁺ T cells (naïve [T_N], effector memory cells [T_{EM}], central memory cells [T_{CM}], terminally differentiated effector memory [T_{EMRA}]) and natural killer T (NKT) cells, but there was no dose-dependent increase in B cells.

4.3 Summary of Nonclinical Experience

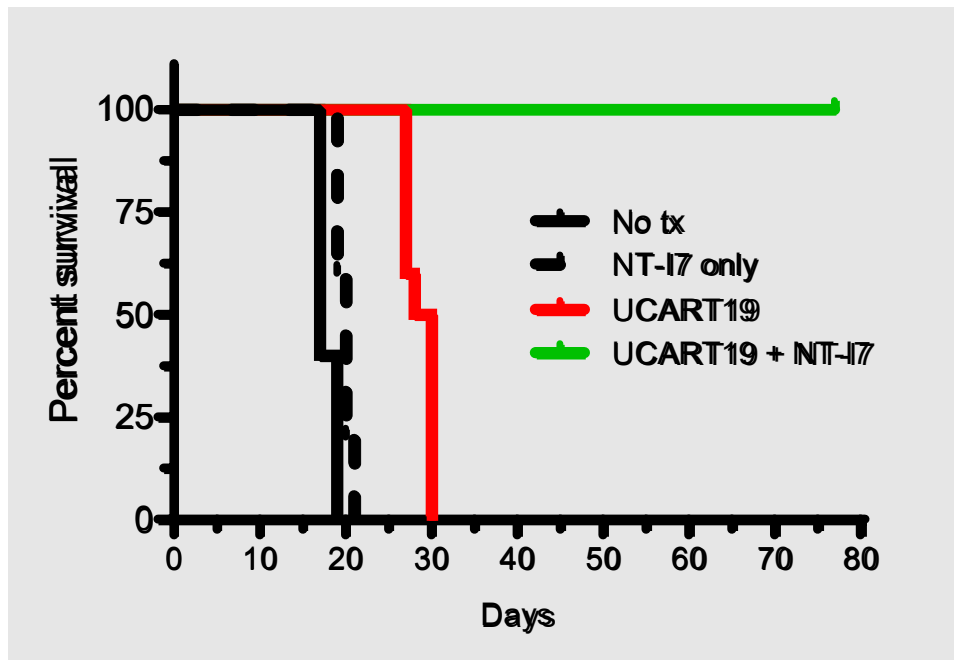
4.3.1 NT-I7 Nonclinical Data with CAR T-cell

4.3.1.1 NT-I7 Treatment Following Universal CAR T-cell (UCART19) Infusion-enhanced CAR T-cell Therapy and Prolonged Survival of UCART19-treated Mice

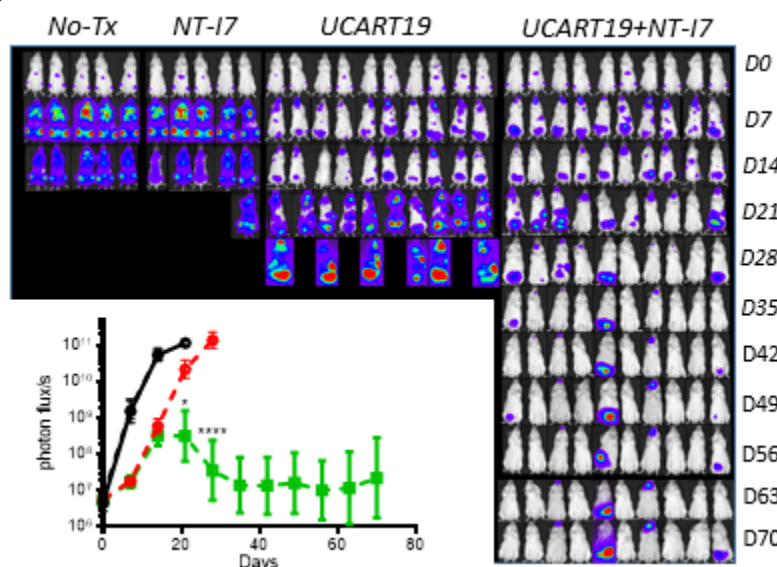
In a CD19⁺ lymphoma xenograft model (NOD-SCID IL2Rgamma^{null} mice implanted with Ramos^{CBR-GFP} cells), while mice treated with anti-CD19 universal CAR T-cell (UCART19) alone (UCART19 group) survived for approximately 29 days, mice treated with UCART19 and NT-I7 (UCART19+NT-I7 group) were still alive at 80 days (Figure 1A) with no mouse showing signs of xenogeneic graft-versus-host disease (GVHD). At 3 weeks post UCART19 infusion, bioluminescent imaging (BLI) revealed minimal tumor signal in UCART19+NT-I7 treated mice and near-undetectable photon flux/s at 4 weeks (Figure 1B).

Figure 1: NT-I7 Effects on UCART19 in Human Lymphoma Model

A



B



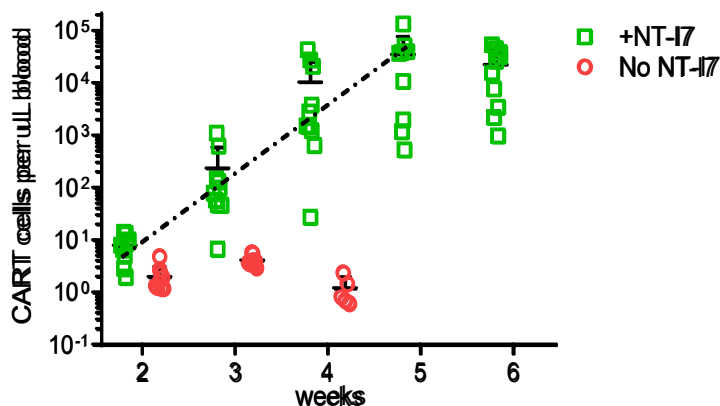
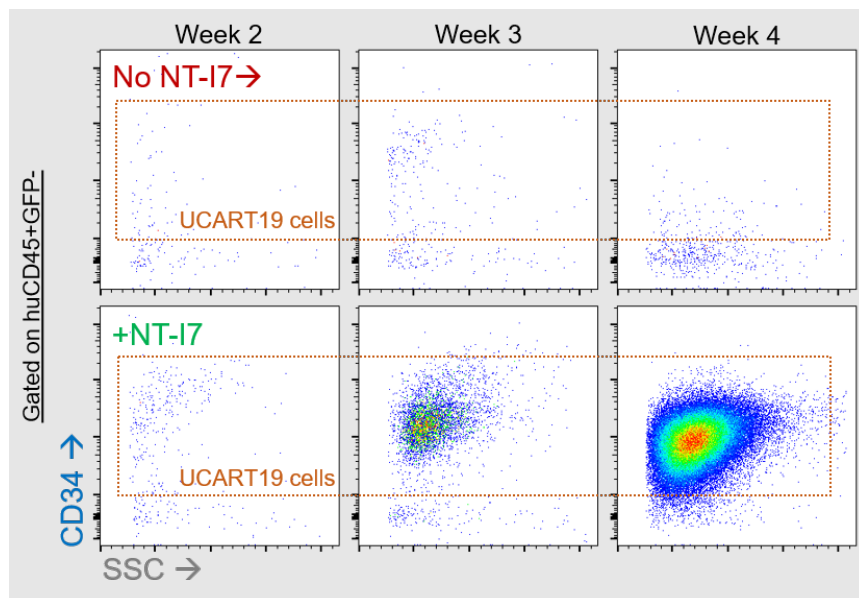
A. NT-I7 prolongs survival of UCART19-treated mice. Mice treated with UCART19 alone (UCART19 group) survived approximately 29 days, while 100% of mice treated with UCART19 and NT-I7 (UCART19+NT-I7 group) were still alive at Day 80, with no mouse showing signs of xenogeneic GVHD (p<0.0001, UCART19+NT-I7 vs. UCART19).

B. NT-I7 enhances CAR-T antitumor efficacy. At 3 weeks post UCART19 infusion, BLI revealed minimal tumor signal in UCART19+NT-I7 treated mice (108 vs. 1010 photon flux/s, p<0.05, UCART19+NT-I7 vs. UCART19) and near-undetectable photon flux/s at 4 weeks (107 vs 1011 photon flux/s, p<0.0001, UCART19+NT-I7 vs. UCART19).

Quantitative 17-parameter flow cytometric analyses of the blood (Figure 2), bone marrow, and spleens (data not shown) revealed an up to ~8000-fold increase in UCART19 cells in NT-I7-

treated mice 4 weeks post UCART19 infusion. These UCART19 cells demonstrated a predominantly effector and effector memory phenotype (data not shown). The increase in CAR-T cells plateaued at approximately Week 5 following combination treatment with NT-17 (Figure 2).

Figure 2: NT-17 Enhances CAR T-cell Expansion and Persistence



Quantitative 17-parameter flow cytometric analyses of blood reveal logarithmic expansion and prolonged persistence of UCART19 cells in mice receiving NT-17.

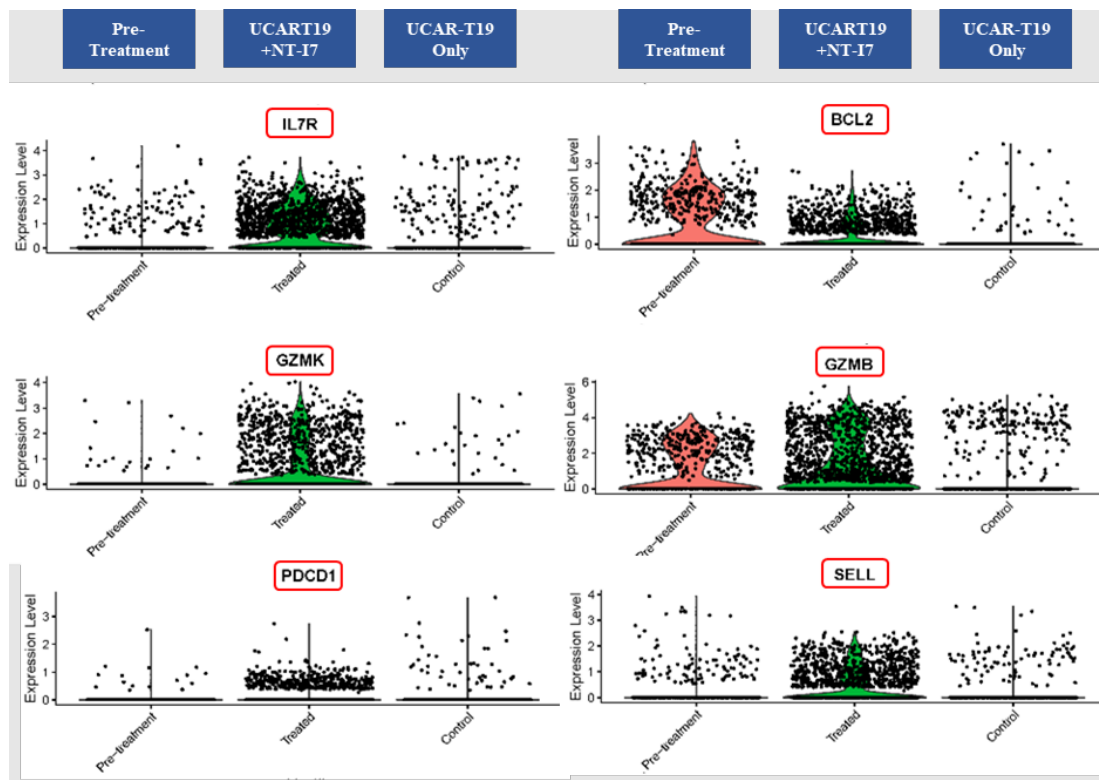
In this nonclinical model of CD19+ lymphoma, addition of NT-17 to UCART19 enhanced UCART proliferation, persistence, and tumor killing, resulting in enhancement of CAR T-cell antitumor efficacy and prolongation of survival.

4.3.1.2 NT-17-induced CAR T-Cells Had Increased Gene Expression of Functional Markers

Single cell analysis of CAR T-cells isolated from mice treated with UCART19 and NT-17 versus with UCART19 only confirmed that NT-17 treatment increased expression of multiple genes that are

related to its functionality, including IL-7 receptor alpha (IL-7R), anti-apoptotic regulator and direct target of IL-7 signaling BCL2, cytolytic lymphocyte-associated serine proteases Granzyme K (GZMK) and Granzyme B (GZMB), and cell adhesion molecule L-Selectin (SELL) (Figure 3).

Figure 3: NT-I7 Treatment Upregulates the Gene Expression of Functional Markers

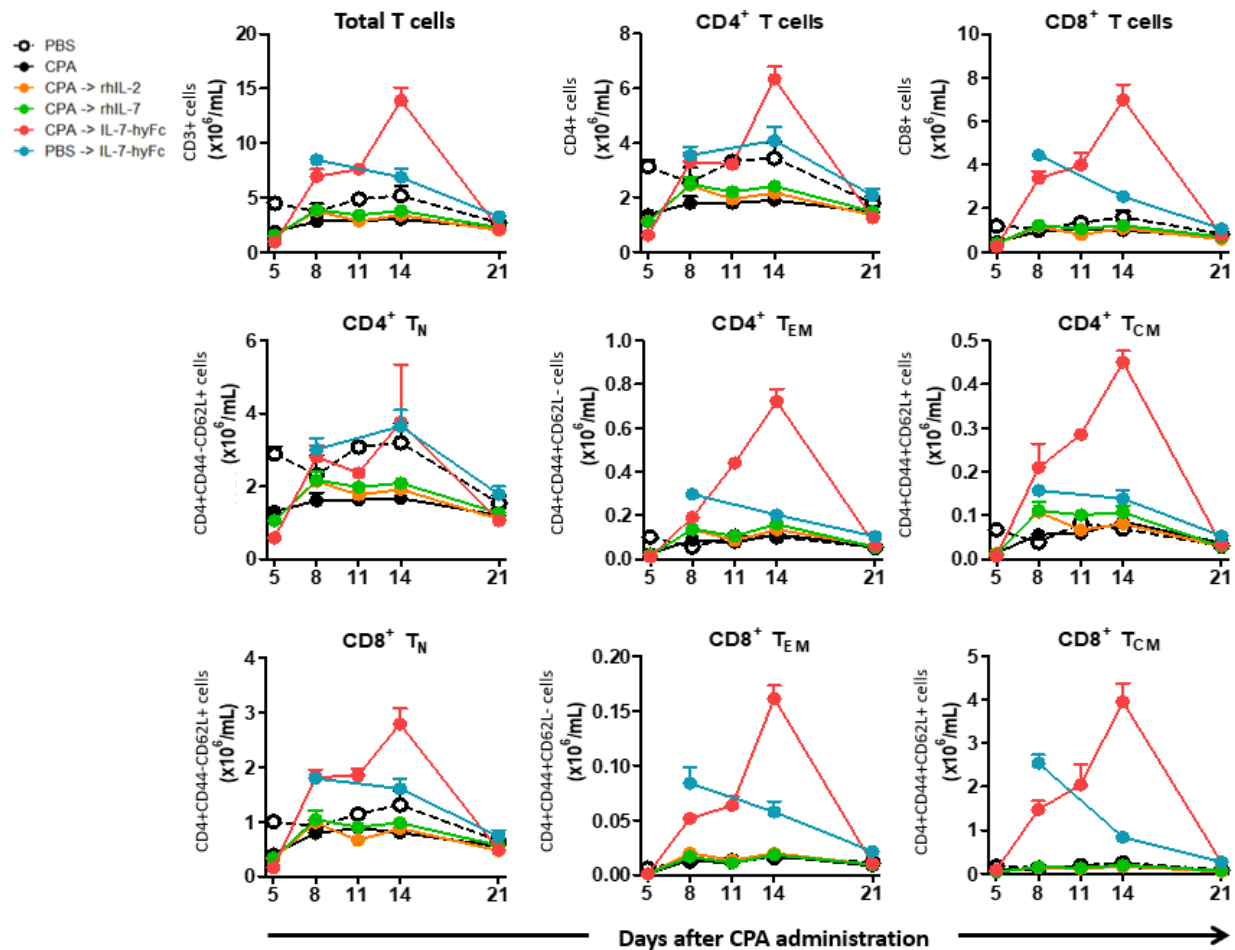


Single cell analysis of CAR T-cells isolated from mice treated with UCART19 + NT-I7 versus with UCART19 only confirmed that NT-I7 treatment increased expression of multiple genes that are related to its functionality. Each dot indicates single MACS-enriched UCART19 cell. IL7R=IL-7R alpha; BCL2=B-cell lymphoma 2, anti-apoptotic molecular and direct target of IL-7 signaling; GZMK=Granzyme K, marker for cytolytic T lymphocytes and natural killer cells; GZMB=Granzyme B, marker for cytotoxic T lymphocytes; PDCD1=programmed cell death 1 (PD-1); SELL=L-selectin, marker for cell surface adhesion molecule.

4.3.1.3 NT-I7 Treatment Resulted in Increased Functional T Cells

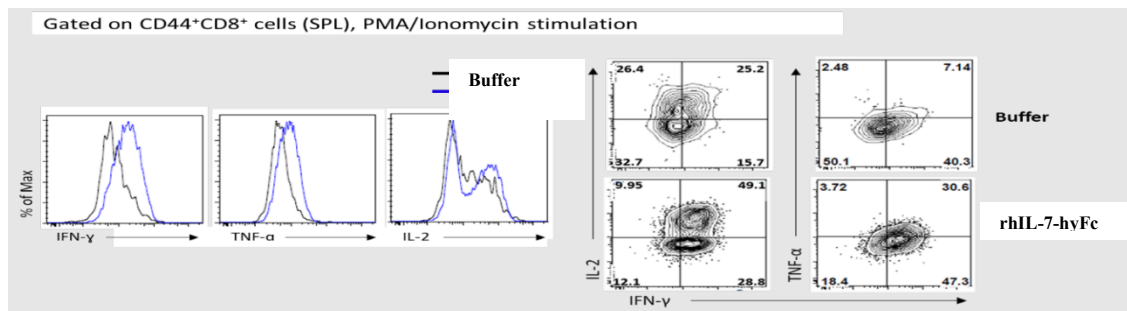
In a cyclophosphamide (CPA)-induced model of lymphopenia, a single NT-I7 treatment increased the number of CD4⁺ T_N, CD4⁺ T_{EM}, and CD4⁺ T_{CM}, with the maximal effect achieved at 2 weeks post-treatment (Figure 4). CD8⁺ T_N, CD8⁺ T_{EM}, and CD8⁺ T_{CM} were also increased, with peak increase at 2 weeks post-treatment (Figure 4).

Figure 4: CPA-induced Lymphopenia Is Reversed by NT-I7 Treatment



Kinetics of lymphocytes counts were analyzed in the peripheral blood after CPA treatment by using the flow cytometry. CD44 and CD62L were also used for gating T lymphocytes subsets same as the data from lymph nodes; T_N (CD44-CD62L+), T_{EM} (CD44+CD62L-), and T_{CM} (CD44+CD62L+) phenotypes. Data are mean $\pm$ SEM.

T-cell functionality (interferon [IFN]- γ , tumor necrosis factor [TNF]- α , and IL-2 expression in CD8⁺ T cells) after NT-I7 or phosphate buffer solution (buffer) treatment was assessed. Compared to the buffer treated control group, CD8⁺ T cells from NT-I7 treated animals showed increased expression of normal T-cell markers of functionality such as IFN- γ , TNF- α , and IL-2 after re-stimulation (Figure 5).

Figure 5: NT-I7 Treatment Increased Expression of IFN- γ and TNF- α in CD8+ T Cells

C57BL/6 mice were treated subcutaneously with 10 mg/kg of NT-I7 or phosphate buffer solution (buffer). On Day 5, splenocytes were isolated and restimulated with T-cell stimulation cocktail containing PMA and Ionomycin with protein transporter inhibitors. Expression of the intracellular cytokines (IFN- γ , TNF- α , and IL-2) in CD8+ T cells was analyzed by flow cytometry.

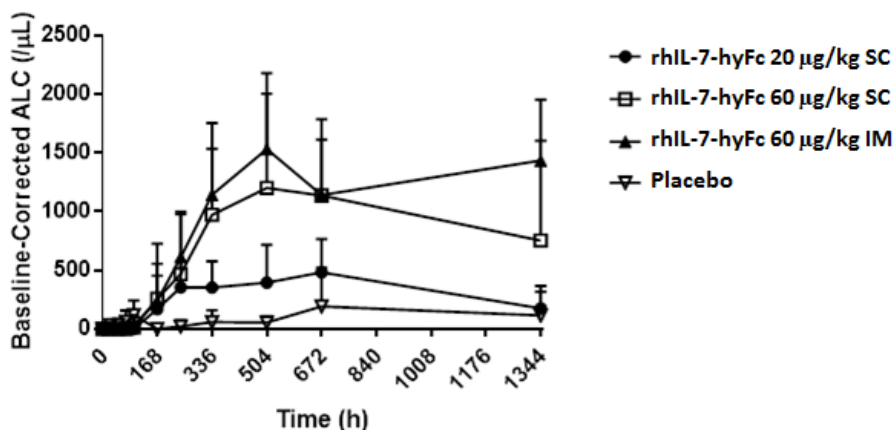
4.4 Summary of Clinical Experience

4.4.1 Clinical Data for NT-I7

4.4.1.1 Clinical Data for NT-I7 in Healthy Volunteers (GX-I7-HV-001)

A first-in-human study in healthy volunteers (HVs) using a single dose of NT-I7 was conducted in South Korea (Study No. GX-I7-HV-001) with doses of 20 μ g/kg (Cohort 1, SC), and 60 μ g/kg (Cohort 2, SC; Cohort 3, IM). Each cohort enrolled 10 HVs, 8 of whom received NT-I7 while the other 2 received placebo. Overall, the treatments were well tolerated. The majority of AEs were mild in intensity, and no death or serious AE was seen during the entire study. The most frequent AE was injection-site reactions, which were mostly Grade 1 and 2 and much milder after IM administration than after SC administration. In addition, NT-I7 was more rapidly absorbed after IM administration than after SC administration (median time to maximum plasma concentration [T_{max}]: 4 hours post dose for IM vs 36 hours post dose for SC), and the exposure to NT-I7 after IM administration was approximately 2 times greater than after SC administration at the same dose of 60 μ g/kg (data not shown). The baseline corrected absolute lymphocyte count (ALC) increase showed a positive correlation with various exposure parameters of NT-I7, providing evidence that observed effects were NT-I7 dependent (Figure 6). Cohort 3 (i.e. 60 μ g /kg IM) results demonstrated that there was a substantial increase in the number of CD4+ and CD8+ T cells, T_N , T_{CM} , T_{EM} , T_{EMRA} cells (Figure 7, Figure 8) and NKT cells, but no increase in the number of B cells, monocytes, or T-regs (data not shown). Based the results from this study, NT-I7 is being given IM in all ongoing clinical studies.

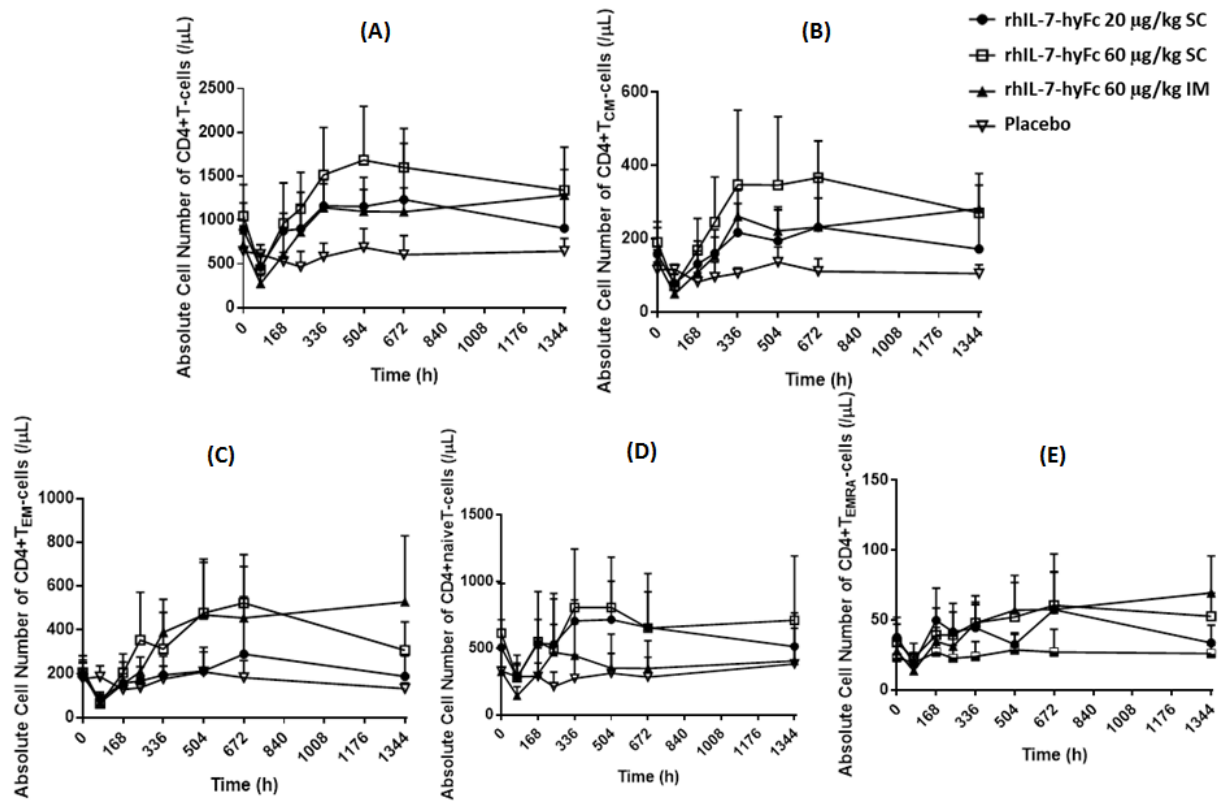
Figure 6: Evidence of NT-17 Pharmacodynamic Effects in Healthy Volunteers



Baseline corrected mean±SD absolute lymphocyte count (ALC) – time profiles after a single SC or IM administration of NT-17 (aka rhIL-7-hyFc) as measured by routine laboratory testing.

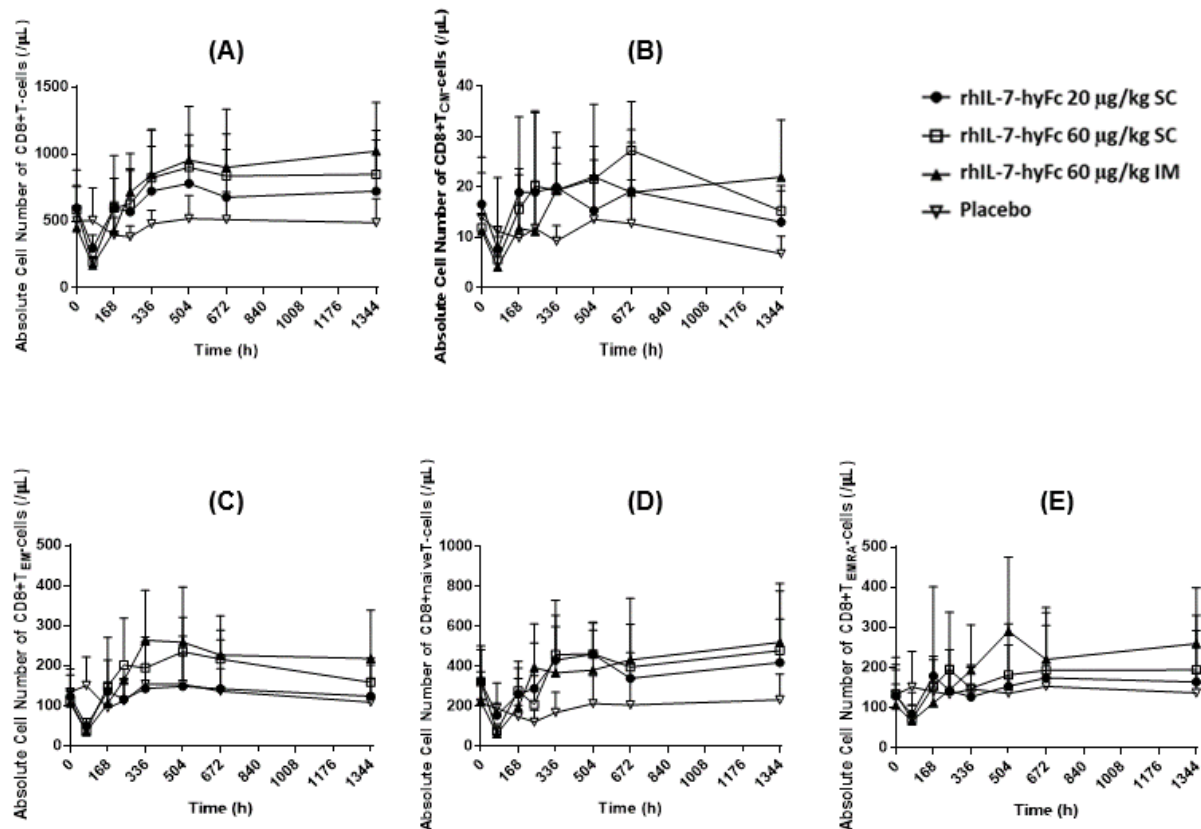
To examine the NT-17 effect specifically on T-cell homeostasis, flow cytometry analysis of PBMCs was performed. The assay was designed to assess the intracellular and cell surface expression of selected markers on PBMCs by comparing the percent change from baseline of subpopulations of lymphocytes that were measured after the drug administration at the following time points: Day -1, Predose, 72h (Day 3), 168h (Day 7), 240h (Day 10), 336h (Day 14), 504h (Day 21), 672h (Day 28) and 1,344h (Day 56) post dose. The specific marker-positive cell number and percentage of total cells were calculated and summarized by cohort using descriptive statistics (Figure 7, Figure 8).

Figure 7: Effect of NT-17 Treatment on CD4+ T-cell Counts



Mean ±SD absolute cell number of (A) CD4+ T cells, (B) CD4+ T_{CM}, (C) CD4+ T_{EM}, (D) CD4+ T_N, (E) CD4+ T_{EMRA}

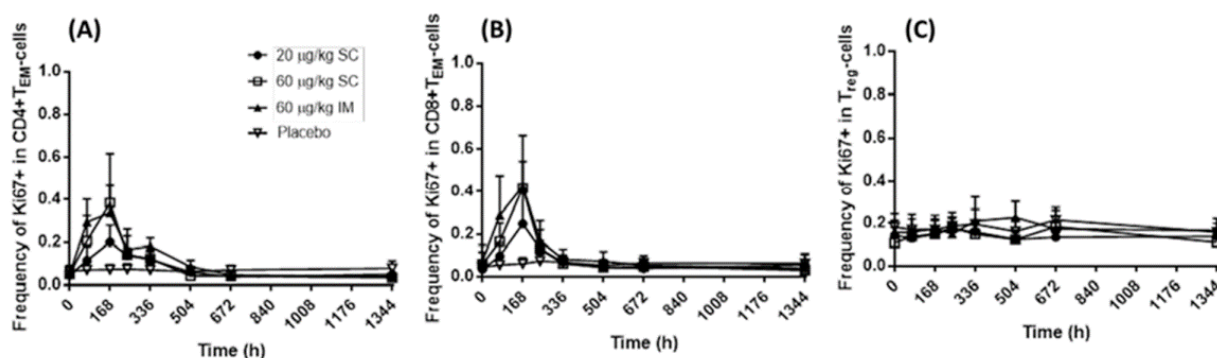
Figure 8: Effect of NT-I7 Treatment on CD8+ T-cell Counts



Mean $\pm$ SD absolute cell number of (A) CD8+T cells, (B) CD8+ T_{CM}, (C) CD8+ T_{EM}, (D) CD8+ naïve T cells, (E) CD8+ T_{EMRA}.

Expression of Ki-67, a marker of cellular proliferation, was also analyzed to verify the impact on cellular proliferation in response to NT-I7 administration. Figure 9 shows that Ki67+ T_N, T_{EM}, T_{CM}, and T_{EMRA} CD4+/CD8+ T cells peaked on Day 7 and returned to baseline levels at approximately 21 to 28 days after a single NT-I7 administration.

Figure 9: Effect of NT-I7 Treatment on Ki-67 Cell Proliferation Marker Expression in T-cell Subsets



Mean $\pm$ SD frequency of Ki-67+ in (A) CD4+, (B) CD8+ T_{EM}, and (C) T-regs. Error bars denote SD.

Collectively, these data provide compelling evidence that NT-I7 treatment increases CD4+ and CD8+ T-cell counts in humans.

NT-I7 is safe and well tolerated overall. Among total subjects, 58 treatment-emergent adverse events (TEAEs) were reported by 26 of 30 subjects (86.7%). In each NT-I7 treatment group, 8 of 8 subjects (100.0%) reported TEAEs as compared with 2 of 6 subjects (33.3%) in the placebo group. The majority of TEAEs were mild in intensity. Most TEAEs were considered probably or possibly related to study drug. There were no serious TEAEs or TEAEs leading to death reported during the study. All TEAEs had resolved by follow-up.

4.4.1.2 Clinical Data for NT-I7 in Patients with Advanced Solid Tumors (GX-I7-CA-003)

A Phase 1b study using multiple IM doses of NT-I7 as a single agent has been completed in South Korea in patients with advanced solid tumors (Study No. GX-I7-CA-003) utilizing a 3+3 dose-escalation approach to determine the recommended Phase 2 dose (RP2D). The dose levels for this study were 60, 120, 240, 480, 720, 960, 1200, and 1700 µg/kg given IM every 3 weeks (q3w). Safety data are summarized below.

A total of 225 TEAEs occurred in 35 subjects (100.0%). By dose group, 14 TEAEs were reported in the NT-I7 60 µg/kg group, 30 TEAEs in the NT-I7 120 µg/kg group, 15 TEAEs in the NT-I7 240 µg/kg group, 21 TEAEs in the NT-I7 480 µg/kg group, 35 TEAEs in the NT-I7 720 µg/kg group, 6 TEAEs in the NT-I7 960 µg/kg group, 88 TEAEs in the NT-I7 1200 µg/kg group, and 16 TEAEs in the 1700 µg/kg group. When the severity of AEs was graded using the NCI-CTCAE (Version 4.0), 118 TEAEs were mild (Grade 1), 84 TEAEs were moderate (Grade 2), 16 TEAEs were severe (Grade 3), and 4 TEAEs were life-threatening or required urgent intervention (Grade 4). Three TEAEs were reported as death related to AEs (Grade 5).

By preferred term (PT), the most common AEs were injection site reactions (61 TEAEs in 25 subjects [71.4%]), pyrexia (26 TEAEs in 15 subjects [42.9%]), and abdominal pain (10 TEAEs in 10 subjects [28.6%]).

There were 6 SAEs in 5 subjects (14.29%): 1 subject in the 120 µg/kg group had Grade 5 mesenteric arterial occlusion (not related to NT-I7); 1 subject in the 480 µg/kg group had Grade 3 ascites and Grade 5 upper gastrointestinal hemorrhage (both not related); 1 subject in the 1200 µg/kg group had Grade 2 azotemia and Grade 5 dyspnea (both not related); and 1 subject in the 1700 µg/kg group had Grade 3 hypersensitivity (related). The last event was also a serious ADR.

There were 10 AEs of special interest (AESI) as specified in the protocol in 5 subjects. The AESI included cases of potential drug-induced liver injury, conditions suggestive of autoimmune disorders, Grade 2 or higher AEs suggestive of hypersensitivity or immune-mediated reaction, Grade 2 or higher hypoxia or dyspnea, and Grade 2 or higher pleural effusion. One AESI (pneumonia) occurred in 2 subjects, all others were reported for a single subject (anaphylactic reaction, hypersensitivity, mesenteric arterial occlusion, pyrexia, hepatic failure, pleural effusion, urticaria, and hypotension).

One of 2 subjects at 1700 µg/kg experienced DLT (hypersensitivity) as specified in the protocol. The RP2D and MTD of NT-I7 was determined to be 1200 µg/kg.

Clinically significant changes in plasma and serum chemistry results after the administration of the study drug were all reported as adverse events or were judged to be due to progression of the underlying disease.

4.4.1.3. Other Studies

ABTC-1403 (also known as NIT-104) is an ongoing Phase 1 dose-escalation and pilot study of the effect of NT-I7 on CD4 cell counts in subjects with high grade gliomas and severe treatment-related CD4 lymphopenia after concurrent radiation therapy (RT) and treatment with temozolomide (TMZ). More details are provided in the *NT-I7 IB*.

NIT-106 is a Phase 1b/2a, open-label study to evaluate anti-tumor efficacy and safety of NT-I7 in combination with anti-PD-L1 (atezolizumab) in subjects with anti-PD-1/PD-L1 naïve or relapsed/refractory high-risk skin cancers. The study is ongoing in the US.

NIT-110 is a Phase 1b/2a, open-label study of NT-I7 in combination with pembrolizumab in adult patients with r/r advanced solid tumors (Basket Trial). The study is ongoing in the US.

NIT-109 is an open-label, randomized, Phase 2 study of NT-I7 in combination with anti-PD-1 (nivolumab) versus nivolumab monotherapy in subjects with advanced or metastatic gastric or gastro-esophageal junction or esophageal adenocarcinoma who progressed on or intolerant to 2 or more prior lines of systemic therapy. The study is ongoing in the US.

No efficacy data are available for any of these studies up to date.

4.5 Benefits and Risks Conclusions

The current safety clinical profile of NT-I7 in treated patients indicates that it is well tolerated. For detailed information about the safety profile of NT-I7 in completed and ongoing studies, please refer to the current version of the NT-I7 Investigator's Brochure.

There is no known benefit at this time; however, an objective of the study is to determine if NT-I7 administration will lead to an increase in the expansion and persistence of CD19 CAR T-cell in-vivo, which may result in increased anti-tumor response rate and improved clinical outcomes.

4.6 Research Hypothesis

We hypothesize that the administration of NT-I7 following standard of care (SOC) CD19 CAR T-cell therapy for subjects with r/r LBCL will be safe, tolerable and may increase the expansion and persistence of CAR T-cells in-vivo, which may result in increased anti-tumor response rate and improved clinical outcomes.

5.0 OBJECTIVES AND ENDPOINTS

This is a phase 1b study evaluating the safety, tolerability, and preliminary anti-tumor activity of NT-I7 (efineptakin alfa), a long-acting human IL-7, post- Kymriah[®], post-Yescarta[®], or post-Breyanzi[®] in subjects with relapsed/refractory large B-cell lymphoma. Specific objectives and corresponding endpoints for the study are outlined in the following Table 1.

Table 1: Objectives and endpoints

Objectives	Corresponding Endpoints
Primary Objectives	
For Dose Escalation Phase: - To evaluate the safety and tolerability of NT-I7 when administered after SOC CAR T-cell Therapy infusion for r/r LBCL - To determine the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D) of NT-I7 when administered after SOC CAR T-cell Therapy infusion for r/r LBCL	- Incidence, nature, and severity of adverse events graded according to NCI CTCAE v5.0, except grading of CRS and ICANS which will be based on ASTCT guidelines. - Incidence and nature of DLTs. - Potential correlation of dose levels with safety and efficacy parameters.
Secondary Objectives	
<u>For Dose Escalation phase:</u> - To explore the preliminary anti-tumor activity of NT-I7 when administered after CAR T-cell Therapy infusion for r/r LBCL based on: - Duration of Response (DOR) - Progression-Free Survival (PFS) - Overall Survival (OS)	Duration of Response (DoR) for the responders defined as the time from the first occurrence of a documented objective response (Partial Response [PR] or Complete Response [CR]) to the time of the first documented disease progression or death from any cause, whichever occurs first, per the Lugano classification (3) as

	determined by the investigator. DoR will be assessed statistically via Kaplan-Meier methods and presented descriptively for the responders. Comparative assessments are not planned on this endpoint. ■ Progression Free Survival (PFS) defined as the time from the first study treatment (Day 1) to the first occurrence of progression or death from any cause, whichever occurs first, per the Lugano classification (3) as determined by the investigator. PFS will be assessed statistically via Kaplan-Meier methods and presented descriptively for all treated subjects; censoring rules and statistical endpoint definitions (time to event) will be detailed in the SAP prospectively. Comparative assessments are not planned on this endpoint. ■ Overall survival (OS) defined as the time from first study treatment
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	(Day 1) to death from any cause. OS will be assessed statistically similarly to PFS (above).
<u>For Dose Escalation and Dose Expansion phases:</u> ○ To continue evaluating the effect of NT-I7 when administered after CAR T-cell Therapy infusion on safety profile ○ The effect of NT-I7 on CAR-T cells expansion	• Rates of grade 3 and higher Cytokine Release Syndrome (CRS) • Rates of grade 3 and higher Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) • Quantitative DNA PCR and/or FACS for CAR-T PK analysis
Exploratory Objectives	
<u>For Dose Escalation and Dose Expansion phases:</u> ○ To make a preliminary assessment of PK parameters of CAR T-cell Therapy when administered NT-I7 post- CAR-T cell therapy	▪ Parameters of expansion, including maximum concentration (C_{max}) and time to maximum concentration (T_{max}) ▪ Parameters of persistence, including the terminal half-life ($T_{1/2}$), last measured concentration (C_{last}), and time of last measured concentration (T_{last}) ▪ Area under the curve for CAR T-cell expansion for days 0-21 (prior to NT-I7 administration), and days 22-100 (after NT-I7 administration and 3 months post CAR T-cell Therapy infusion)

○ To evaluate the immunogenicity of NT-I7 ○ To evaluate the Pharmacokinetic profile of NT-I7 For the Dose Expansion phase: ○ To explore the Overall Response Rate (ORR) of NT-I7 when administered after SOC CAR T-cell Therapy infusion for r/r LBCL Exploratory Objectives for Correlative Analysis For Dose Escalation and Dose Expansion phases: ○ To evaluate the effect of NT-I7 when administered after CAR T-cell Therapy on the expansion of lymphocytes, CAR T-cells, and serum cytokines in vivo	▪ Incidence of anti-drug antibody (ADA) to NT-I7 during the study relative to Day 21 (pre-dose NT-I7) ▪ Serum concentration of NT-I7 administered on Day 21 pre-dose and at specified timepoints for the following parameters: Area under the concentration time-curve (AUC), maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), and clearance (CL). ▪ Overall Response Rate (ORR) at 3 months as assessed by Investigators using FDG PET-CT and the Lugano classification (3) • Flow cytometry-based comprehensive immunophenotyping of T cells, T-cell subtypes and myeloid subsets in peripheral blood. Additional markers may include, but are not limited to, Ki-67.
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For Dose Escalation phase: ○ To correlate baseline and post-treatment responses	• Quantitative DNA PCR and/or FACS for measuring CAR T-cell expansion • Plasma cytokine profiling • Single cell RNA sequencing (scRNA-seq) of peripheral blood before NT-I7 administration, on D35 +/- 2 days (i.e., approximately 2 weeks after NT-I7 administration), and at the time of relapse • LBCL immunophenotyping pre-treatment (before CAR T-cell Therapy infusion) and at the time of relapse • Polyfunctional analyses to assess the number and percentage of CAR T-cell and non-transduced T cells that are able to express and secrete various cytokines and chemokines before NT-I7 administration and on D35 +/- 2 days • Plasma Minimum Residual Disease (MRD), and compared to SOC FDG PET-CT imaging
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6.0 SUBJECT SELECTION

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet entry criteria. No protocol eligibility waivers will be granted.

6.1. Inclusion Criteria

Subjects must meet all the following criteria for study entry:

1. Must be ≥ 18 years on the day of signing informed consent.
2. Be willing and able to provide written informed consent/assent for the study.
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1
4. Subjects should be eligible for CAR-T therapy respective to the current FDA-approved CAR-T label for Yescarta, Breyanzi, or Kymriah.
5. Subjects with histologically confirmed relapsed or refractory LBCL including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high grade B-cell lymphoma, DLBCL arising from follicular lymphoma, and primary mediastinal large B-cell lymphoma, must be eligible for SOC CD19 CAR T-cell Therapy.
 - (a) Tumor tissue (fresh or archival) must have been tested to confirm the type of LBCL.
6. Subjects must have measurable disease by IWG response criteria for lymphoma [Lugano classification (3)]
 - (a) Baseline fluorodeoxyglucose (FDG)-PET/computed tomography (CT) scans must show positive lesions compatible with CT-defined anatomical tumor sites but will not be used in subsequent clinical decisions.
 - (b) A previously irradiated lesion can be considered a target lesion if the lesion is well defined, measurable, and has clearly progressed.
 - (c) Subjects that received bridging therapy pre-lymphodepletion will be allowed for enrollment regardless of re-staging results (PMR or CMR), even if the lesion is not measurable per the criteria mentioned above.
 - (d) PET/CT scans done as SOC up to 28 days pre-lymphodepletion therapy will be allowed. All subjects whose scans are > 28 days from lymphodepletion therapy will need a re-staging FDG-PET/CT scan.
7. (This is a placeholder for inclusion criterion 7, which has been removed.)
8. Subjects must have a life expectancy of greater than or equal to 12 weeks per assessment from the enrolling physician.
9. Adequate organ and marrow function per institutional guidelines **at the start of lymphodepleting chemotherapy as pre-conditioning for SOC CD19 CAR T-cell infusion.** The following laboratory parameters (9a-h) are recommendations. Labs outside of these ranges may be considered for inclusion after consultation with the medical monitor. Cytopenia resulting from disease or bridging therapy will not be considered exclusionary.
 - a. Hemoglobin ≥ 8.0 g/dL or ≥ 4.96 mmol/L
 - b. Absolute neutrophil count $\geq 1,000/\mu\text{L}$
 - c. Platelets $> 50,000/\mu\text{L}$
 - d. Total bilirubin $\leq 1.5 \times$ institutional upper limit of normal (ULN) OR direct bilirubin $\leq$ ULN for subjects with total bilirubin levels $> 1.5 \times$ ULN, except subject with documented Gilbert's syndrome ($> 3 \times$ ULN), who must have a baseline total bilirubin ≤ 3.0 mg/dL

- e. $\text{AST(SGOT)/ALT(SGPT)} \leq 2.5 \times \text{ULN}$ ($\text{AST and/or ALT} \leq 5 \times \text{ULN}$ for subjects with liver metastasis)
 - f. Alkaline phosphatase $\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ for subjects with documented liver involvement or bone metastases)
 - g. Creatinine clearance (CrCl) $\geq 30 \text{ mL/min}$ as calculated per institutional standard.
 - h. $\text{INR and aPTT} \leq 1.5 \times \text{ULN}$ unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
10. Female subjects who are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks; female subjects of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or to use dual methods of contraception for the duration of study treatment and for 90 days after NT-17 injection, whichever is longer. Female subjects of childbearing potential (including women who have had a tubal ligation) must have a negative serum or urine pregnancy test within 72 hours prior to NT-17 injection. If the urine test is positive, or cannot be confirmed as negative, a serum pregnancy test will be required.
11. ECG demonstrating Fridericia's corrected QT interval (QTcF) $< 500 \text{ ms}$. Patients with $\text{QTcF} \geq 500 \text{ ms}$ will require clearance by a local cardiologist.

6.2. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for enrollment in the study:

- 1. In Dose Escalation phase: Grade ≥ 3 CRS or ICANS post-CD19 CAR T-cell infusion. Note: Grade 1 or 2 CRS or ICANS must be completely resolved >3 days **prior to NT-17 injection**
- 2. In Dose Expansion phase: Grade ≥ 3 CRS or ICANS post-CD19 CAR T-cell infusion. Note: Grade 1 or 2 CRS or ICANS must be completely resolved >3 days **prior to NT-17 injection**
- 3. Pregnant, lactating or breastfeeding or expecting to conceive or father children within the study duration from screening through 120 days after the last dose of study treatment.
- 4. This exclusion criteria has been removed and remains as a placeholder.
- 5. Subjects with documented current central nervous system (CNS) involvement by lymphoma are to be excluded from study participation.
- 6. Any concurrent chemotherapy or biologic or hormonal therapy for cancer treatment. Note: Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. In addition, local treatment (eg, by local surgery or radiotherapy) of isolated lesions for palliative intent is acceptable beyond the DLT evaluation period with prior consultation and agreement with the medical monitor.
- 7. Subjects who have autoimmune disease history for the past 2 years, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barre syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. The following are exceptions to this criterion:
 - (a) Subjects with vitiligo or alopecia.
 - (b) Subjects with type 1 diabetes mellitus.
 - (c) Subjects with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement.

- (d) Psoriasis not requiring systemic treatment.
- (e) NOTE: Diverticulitis that is not associated with inflammatory bowel disease is not considered exclusionary (e.g., subjects who do not have active diarrhea due to chronic diverticulitis).
- 8. Have active and clinically relevant bacterial, fungal, viral, or TB infection, including known Hepatitis A, B, or C or HIV (testing not required).
- 9. Concurrent enrollment in another clinical study unless it is an observational (noninterventive) clinical study.
- 10. Receipt of any conventional or investigational anticancer therapy, not otherwise specified above, within 30 days prior to NT-17 injection.
- 11. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to NCI CTCAE v5.0 Grade ≤ 1 with the exception of alopecia and laboratory values listed per the inclusion criteria. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by any of the investigational products may be included (e.g., hearing loss, peripheral neuropathy) after consultation with the medical monitor.
- 12. Receipt of live, attenuated vaccine within 30 days prior to NT-17 injection. Note: Subjects, if enrolled, should not receive live vaccine during the study and through 30 days after NT-17 injection, whichever is longer. The administration of killed vaccines is permitted at any time.
- 13. Has had an allogeneic tissue/solid organ transplant or bone marrow transplant.
- 14. Subjects for whom intramuscular therapy is contraindicated.
- 15. Has clinically significant cardiac disease, including, but not limited to, any of the following:
 - 1) Uncontrolled atrial fibrillation
 - 2) Congestive Heart Failure NYHA Class ≥ 2
 - 3) Or any of the following **within 6 months prior to Baseline, Day 0 CAR-T administration:**
 - Unstable angina
 - Myocardial infarction
 - Coronary artery bypass grafting
 - Coronary angioplasty
 - Coronary stenting
 - Clinically significant cardiac arrhythmia and/or conduction abnormality
 - 4) History of other clinically significant cardiac disease that, in the opinion of the Investigator or designee, is a contraindication to study treatment is also excluded.

6.3 Inclusion of Women and Minorities

Men and women of all races and ethnic groups are eligible for this study.

6.4 Meals and Dietary Restrictions

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6.5 Contraception and Breast Feeding

NT-I7 may have adverse effects on a fetus in utero. Furthermore, it is not known if NT-I7 has transient adverse effects on the composition of sperm, and there are no available data on the use of NT-I7 in pregnant or breastfeeding women. Subjects will be counseled on the possible risks related to pregnancy, including possible prolonged risks of reproductive toxicity, and must agree not to become pregnant, breastfeed a baby, father a child, or donate sperm within 90 days after receiving the study agent. Subjects of reproductive potential must agree to the study birth control requirements ([Section 6.1](#)).

If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

7.0 STUDY DESIGN

7.1 Overall Design

This is a multicenter Phase 1b study evaluating the safety, tolerability, and preliminary anti-tumor activity of NT-I7 administration following SOC CD19 CAR T-cell therapy for eligible subjects with r/r LBCL. The study consists of a Dose Escalation phase followed by a Dose Expansion phase.

In the Dose Escalation phase (see [Section 7.1.1](#) for details), subjects will be enrolled in 1 of 7 dose levels, starting with 60 µg/kg and up to 720 µg/kg. Intermediate dose levels between 60 µg/kg and 720 µg/kg may be explored depending on emerging clinical data.

A dose schedule for an individual dose level will not be taken into expansion until the Dose Escalation phase has been completed or a maximum tolerated dose (MTD) has been determined, whichever occurs first.

In the Dose Expansion phase (see [Section 7.1.2](#) for details), up to 15 subjects will be enrolled and treated with the recommended dose identified in the Dose Escalation phase.

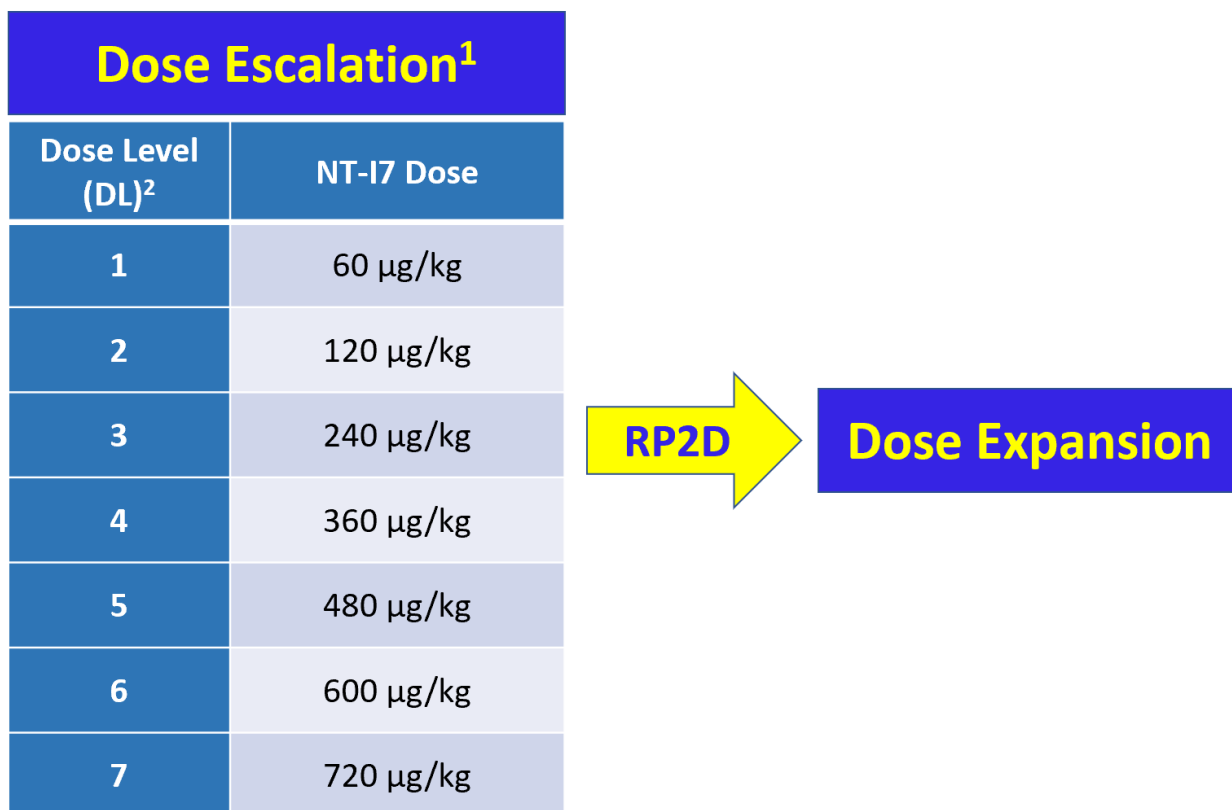
Up to 17- 42 subjects in the Dose Escalation phase, and up to 15 subjects in the Dose Expansion phase will be enrolled at approximately 20 study centers.

A screen failure subject is defined as a subject that is consented and screened but does not qualify to be part of the SOC CAR T-cell Therapy for this study (for any reason).

An enrollment failure is defined as a subject that is consented and screened, lymphodepletion is performed, SOC CAR T-cell Therapy is administered, but the subject is not eligible to receive NT-I7 (for any reason).

The Treatment Schema is illustrated in [Figure 10: Treatment Schema](#).

Figure 10: Treatment Schema



¹ DL 1-2: accelerated escalation (1 subject/DL); DL 3-7: 3+3 design

² Intermediate DLs between 60 µg/kg and 720 µg/kg may be explored based on emerging data

7.1.1. Dose Escalation phase

The Dose Escalation phase is designed to assess the safety and tolerability, including determination of the MTD and/or the RP2D, of NT-17 when administered after SOC CAR T-cell infusion for r/r LBCL. Seven dose levels (DL) are planned: the starting DL (DL1) will be 60 µg/kg, and the highest DL to be tested (DL7) will be 720 µg/kg, as outlined in the Treatment Schema. Other intermediate DLs between 60 µg/kg and 720 µg/kg may be explored based on emerging data.

The Dose Escalation phase will begin with an accelerated phase with 1 subject per cohort at the first 2 DLs (DL1 = 60 µg/kg and DL2 = 120 µg/kg), followed by a standard 3+3 design on the remaining 5 DLs (see Treatment Schema), each with a cohort of 3 independent subjects each time and with a maximum total of 6 subjects per cohort. If at least 2 Grade ≥2 AEs or any 1 Dose Limiting Toxicity (DLT) are observed in the single subject enrolled in either DL1 or DL2, the accelerated phase will convert to a conventional 3+3 design at the DL where the AEs or DLT are observed and remain so for all the DLs above. In addition to converting to the 3+3 design, the next DL will not exceed 50%

of the previous DL. Similarly, if a 2nd DLT occurs in a DL, the next DL in the escalation scheme will not exceed 33% of the previous DL.

In all DLs that followed the 3+3 design in DL1-5, subjects were dosed in a 3-week staggered fashion: the 1st subject in a DL was monitored for 3 weeks; after 3 weeks, if the safety is acceptable, the 2nd subject was enrolled and treated at that same DL; similarly, the 3rd subject was enrolled and treated only if the safety appeared to be acceptable for both the 1st and 2nd subjects after the 2nd subject had been monitored for 3 weeks. If additional subjects were required for a DL, they would be enrolled and treated in similar 3-week staggered fashion.

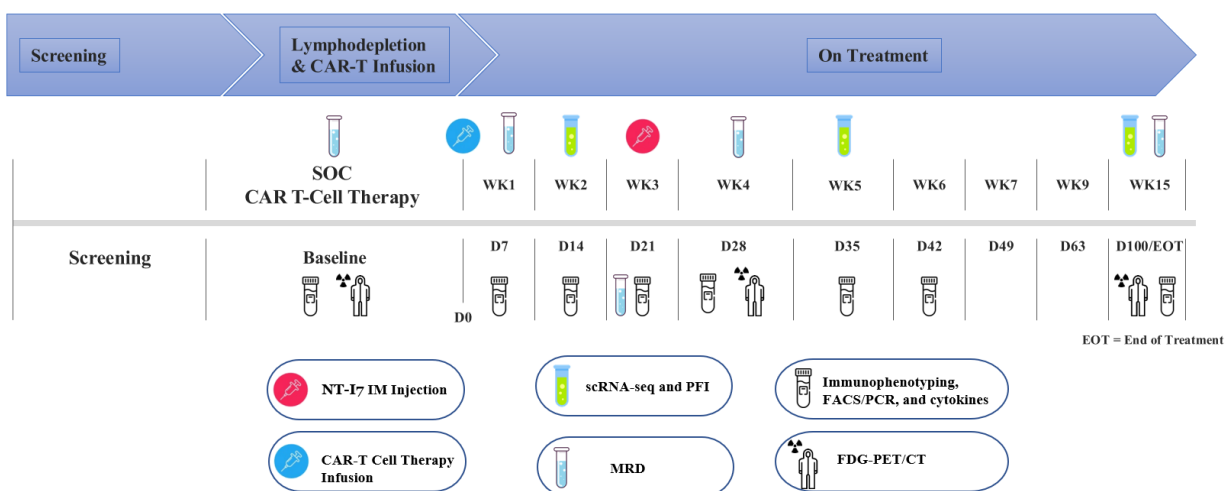
No DLTs were observed in DL1-5. There was no subject at any dose level who experienced the first ADR between 14 days to 21 days after NT-I7 administration. Given these results, starting at Dose Level 6, if a DLT is not observed in the first subject after 2 weeks, then the second and third subjects can be dosed simultaneously. The DSMC will occur once the final subject in a cohort has completed the 3-week DLT period.

7.1.2. Dose Expansion phase

Once RP2D has been determined from the Dose Escalation phase, up to 15 subjects will be enrolled in the Dose Expansion phase and treated at the RP2D to further evaluate the safety and preliminary anti-tumor activity of NT-I7 administration following SOC CD19 CAR T-cell therapy for eligible subjects with r/r LBCL. Subjects in Dose Expansion can enroll simultaneously.

The Study Design Schema is outlined below in [Figure 11](#).

Figure 11: Study Design Schema



7.2. Dose-Limiting Toxicity (DLT)

All toxicities will be graded using NCI-CTCAE Version 5.0, with the exception of CRS and ICANS which will be graded using ASTCT guideline. For the purpose of this study, a DLT is any event attributed to NT-I7 and occurring during the DLT period of the first 21 days after NT-I7 injection.

Dose-limiting toxicity is defined as any AE occurring within the first 21 days after NT-I7 injection that is considered to be at least possibly, probably, or definitely related to the study treatment (NT-I7) per the investigator, and that meets at least one of the non-hematologic or hematologic criteria listed below.

Hematologic criteria

- Any Grade 5 toxicity
- Grade 4 neutropenia lasting more than 5 days
- Febrile neutropenia of more than 5 days ($ANC < 1.0 \times 10^9/L$, fever $\geq 38.5^\circ C$)
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding or
- Any requirement for platelet transfusion not recovering to baseline at the end of DLT period
- Grade 4 anemia, unexplained by underlying disease
- Grade 4 hematological toxicities lasting more than 21 days

Non-hematologic criteria

- Any Grade 5 toxicity
- Grade 3 or higher non-hematologic toxicity.
- Hy's law criteria
- Any Grade ≥ 4 CRS or Grade 3 CRS that does not improved to Grade ≤ 1 within 72 hours
- Any Grade ≥ 3 ICANS. Note: Grading of CRS and ICANS is based on ASTCT guidelines

The following exceptions are acceptable (i.e., not considered DLTs).

- Grade 3 or 4 electrolyte abnormalities that lasts < 24 hours to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- Grade 3 nausea, vomiting or diarrhea that resolves to Grade 2 or less within 72 hours with symptomatic treatment
- Grade 3 liver enzyme abnormalities improving to grade 2 or better within 72 hours

Once all subjects in a dose level have completed the 3-week (21 days) DLT window, the AEs will be assessed by the DSMC, which includes the Protocol PI, Study Medical Monitor, Study Statistician, and Study Sponsor's CMO or designee.

The subjects must complete the full 3-week DLT window to be considered evaluable for DLTs. Subjects who discontinue from the study before completion of the full 3-week DLT window for reasons other than the occurrence of a DLT (e.g., withdrawal of consent, rapid tumor progression, death due to rapid tumor progression, AE that does not meet DLT criteria) will not be considered evaluable for DLTs and will be replaced.

All subjects will be monitored for occurrence of DLT. Monitoring of all safety and toxicity data is done by the PIs, the study Sponsor and/or designee on a real-time basis as data are entered into the electronic data capture (EDC) system. All participating sites must notify the protocol PI and the Sponsor or designee when a DLT has occurred.

7.3. Study Stopping Rules (applicable to both Dose Escalation and Dose Expansion phases)

These rules are applicable to all subjects that are considered enrolled and have received NT-I7:

- Any Grade 5 adverse event (except for events related to disease progression or clearly unrelated deaths); OR
- Any Grade 4 or life-threatening toxicity attributable to NT-I7 that is unmanageable and unexpected; OR
- Subject incidence of > 33% for any of the following events regardless of duration (including all subjects from Dose Escalation and Dose Expansion):
 - Grade 4 CRS
 - Grade 4 vital organ toxicity
 - Grade 3 or higher ICANS
 - Other nonhematologic serious adverse event
 - New malignancy (distinct from recurrence/progression of previously treated malignancy)

7.4. Maximum Tolerated Dose (MTD)

The MTD is defined as the highest dose within a cohort where no more than 1 of 6 subjects experiences a DLT. This will be determined during the Dose Escalation phase based on the assessment of DLTs during the DLT evaluation period, as defined in [Section 7.2](#).

7.5. Determination of the RP2D

The RP2D will be based on an accumulation of all available data. All available clinical PK, PD, anti-tumor activity (including best ORR) and safety, and nonclinical pharmacology data will be pooled. Integrated dose-response and exposure-response analyses will be conducted to determine the RP2D.

7.6. Rationale for Dose Selection

A Phase 1b study using multiple IM doses of NT-I7 as a single agent was conducted in South Korea in subjects with advanced solid tumors (Study No. GX-I7-CA-003). The dose levels for this study include 60 µg/kg, 120 µg/kg, 240 µg/kg, 480 µg/kg, 720 µg/kg, 960 µg/kg and 1200 µg/kg given IM every 3 weeks (Q3W). Dose levels up to 1700 µg/kg have been tested. A total of 35 patients were enrolled and treated with NT-I7. There were 3 subjects who had AEs that resulted in death; none were considered related to NT-I7. Five subjects had 6 cases that were reported as SAEs. One of these SAEs was also a serious adverse drug reaction (ADR). The most common treatment-related AEs were injection site reactions, pyrexia, and abdominal pain. Dose-limiting toxicity (DLT) was reported in 1

of 2 subjects in the 1700 µg/kg dose group. The RP2D and maximum tolerated dose (MTD) were determined to be 1200 µg/kg.

Pharmacodynamic data from the study showed ALC and naïve / less-differentiated memory subsets of CD4+ and CD8+ T cells increased in a dose-dependent manner after NT-I7 administration. The levels of endogenous IL-7 remained at normal levels without any significant change. Pharmacokinetic data show that C_{max} and AUC_{last} increased in a dose-proportional manner. The study confirmed that NT-I7 was safe and tolerated in patients with cancer, and that it can be safely administered without risk of cytokine storm when used in combination with other anticancer drugs.

However, since the safety of NT-I7 given after CAR T-cell Therapy infusion in subjects with r/r LBCL is not known, 60 µg/kg is selected as the starting dose and 720 µg/kg will be the highest dose level to be tested in this study.

7.7. Rationale for Timing of NT-I7 Injection

Data from the JULIET study showed that the risk of CRS and ICANS development is greatest during the first 14 days post Kymriah infusion, specifically: 1) Median onset of CRS was Day 3, with all but one case had onset ≤ 9 days after Kymriah infusion; median duration of CRS was 7 days; 2) Median onset of neurotoxicity was Day 5 with median time to resolution of 14 days; 3) Median time to maximum transgene level (for tracking of CAR T-cells) was 10 days.

Results were similar in the ZUMA-7 study, with a higher risk of CRS and ICANS development during the first 10-14 days post Yescarta. Following similar patterns, the median onset of CRS post-Yescarta was Day 3 (range 1 to 10) and median duration of CRS was 7 days. Median onset (Day 7) and duration of neurotoxicity (9 days) are also comparable between Yescarta and Kymriah SOC.

At the TRANSCEND trial, Breyanzi showed a slightly better safety profile, with median CRS onset at Day 5 and only 5 days for median CRS duration. Median onset (Day 9) of neurotoxicity is also slightly delayed in Breyanzi, while neurotoxicity median duration (11 days) is comparable between all CAR-T SOC. (20)

Additionally, it has been shown that at 3 months post-intensive chemotherapy, mean CD8+ T-cell number returned to the baseline, whereas mean CD4+ T-cell number was only 35% of pretherapy values. Further, at 3 months posttherapy, there was no relationship between age and CD8+ T-cell number whereas CD4+ T-cell number was inversely related to age. There were no apparent differences in CD8+ recovery among patients with or without thymic enlargement, while CD4+ recovery was enhanced in patients with thymic enlargement after chemotherapy. Therefore, thymic-independent pathways of T-cell regeneration appear to rapidly regenerate substantial numbers of CD8+ T cells, but not CD4+ T cells, resulting in prolonged CD4+ T-cell lymphopenia after T-cell depletion by chemotherapy. These results suggest that therapies that can increase proliferation of T cells in general and CD4+ T cells in particular, such as NT-I7, could lead to rapid T-cell reconstitution and thereby potentially provide clinical benefits to patients.

Thus, NT-I7 administration will be given 21 days after SOC CD19 CAR T-cell infusion (D21 +/- 2 days) in order to avoid the potential exacerbation of CRS and ICANS, and at the same time maximize the potential to increase the infused CAR T-cells and the subject's endogenous T cells.

7.8. Rationale for 2-week Staggered Dosing and 3-week DLT Period

NT-I7 PK data shows that in the dosing range for the NIT-112 study (60 – 720 µg/kg) the maximum serum concentration is reached within the first 24 hours and NT-I7 is almost undetectable in serum by Day 7 (168 hours). In both DL3 and DL4, by Day 7 the NT-I7 serum concentration had decreased by 2 orders of magnitude and was close to the limit of detection. In addition, accumulated NIT data across indications shows that the low NT-I7 serum concentration by Day 7 is consistent in a wide range of dose levels, up to the maximum dose planned for the NIT-112 study (720 µg/kg). Anti-drug antibodies (ADA) against NT-I7 have also not been detected in any of the dosed subjects and immunogenicity is not a concern. There was no CRS or ICANS related to NT-I7 in subjects that participated in DL1-5. No DLTs were observed from DL1-5. In addition, 87% of ADRs occurred within 13 days after NT-I7, and no subject at any dose level experienced the first ADR between 14 days to 21 days after NT-I7 administration. Given this data, starting at DL6, if a DLT is not observed in the first subject after 2 weeks, then the second and third subjects in the cohort can be dosed simultaneously. The DSMC will occur once the final subject in a cohort has completed the 3-week DLT period.

7.9. Disease Assessments

Prior studies evaluating recombinant human IL-7 have reported spleen and lymph nodes increased both in size and FDG uptake following rhIL-7 administration and remained elevated above baseline for 8 weeks. Additionally, recent data have demonstrated improved specificity and similar sensitivity of Immunoglobulin High-Throughput Sequencing (Ig-HTS) of plasma (cell-free DNA) for minimal residual disease (MRD) surveillance compared to SOC FDG PET-CT in DLBCL. Therefore, in order to effectively monitor early disease response following CAR-T and NT-I7 treatment, subjects will be assessed at baseline, 1 month and 3 months with FDG PET-CT and at baseline, D7, D21, D28, and D100 with plasma MRD. Tumor assessment with FDG PET-CT or CT as SOC will be performed at 6 months and 12 months post-CAR T-cell Therapy during survival follow-up.

The results of FDG PET-CT and CT scans will be reviewed and assessed by the Investigators using the Lugano classification (3).

7.10. Treatment Plan

7.10.1 NT-I7 (aka rhIL-7-hyFc, efineptakin alpha)

NT-I7 will be administered as an intramuscular (IM) injection at the appropriate DL for each cohort. Each subject will receive only one NT-I7 injection administered on Day 21 +/-2 days (post-CAR T-cell Therapy infusion). Subjects will be hospitalized for NT-I7 injection and monitored for at least 24 hours after NT-I7 injection. If subjects develop Grade 2 or higher AEs, subjects will remain hospitalized until resolution of AEs to grade 1 or better. Subjects can be kept in the hospital longer at the discretion of the treating physicians.

7.10.2 Kymriah®

Kymriah will be administered per manufacturer's recommendations and in accordance with FDA prescribing guidelines and best institutional practices for SOC use.

7.10.3 Yescarta®

Yescarta will be administered per manufacturer's recommendations and in accordance with FDA prescribing guidelines and best institutional practices for SOC use.

7.10.4 Breyanzi®

Breyanzi will be administered per manufacturer's recommendations and in accordance with FDA prescribing guidelines and best institutional practices for SOC use.

7.10.5 Duration of Treatment, Study and Follow-up

The enrollment date is at the start of NT-I7 treatment. The duration on study will be approximately 3 months following NT-I7. Subjects will then be followed up per standard of care and per the REMS program for the SOC CD19 CAR T-cell Therapy given.

7.11. Duration of Follow-Up

The End of Study (EOS) visit is defined as Day 100. An EOS visit should be completed in all subjects who terminate before Day 100. Subjects will continue to be followed in survival follow-up until the end of the study which is defined as 3 months after the final subject is enrolled or the sponsor stops the study, whichever occurs first.

Subjects who permanently discontinue the end of study for reasons other than disease progression are recommended to have imaging scans performed at SOC intervals at 6- months and 12- months post CAR T-cell Therapy administration, at the investigative site or locally, up to one year after discontinuation of study treatment. Standard of care disease assessments will be collected until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent or end of study, whichever occurs first.

After disease progression or start of new anticancer treatment, subjects will be followed for survival every 90 days ($\pm$ 7 days) from the date NT-I7 was given until death, lost to follow-up, withdrawal of consent or end of the study, whichever occurs first. Survival follow-up can be done either by in-person visit or by telephone assessment.

Subjects removed from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE; in addition, the subjects will be followed for disease status and overall survival, as described above.

Subjects that are withdrawn or withdraw consent should be offered the opportunity to partially withdraw from the trial in one of two ways: 1) to partially withdraw from portions of the active trial,

but allow continuation of safety followup visits and procedures, or 2) to partially withdraw and only allow continued data collection through their medical chart or contact with a provider, not following the study schedule. A note should be entered into the subject's medical and/or research records indicating whether the subject agreed to this at consent and continues to agree at time of withdrawal. In the first case, protocol deviations will be administered for out of window visits or missed procedures. In the second case, data collected will be recorded, including survival status (alive or dead), cause of death, AE/SAEs as per sections [12.3.1](#) and [12.3.2](#), new anti-cancer therapies, and SOC FDG-PET scans. For these subjects, protocol deviations will not be administered, as the study schedule and procedures are not being followed.

7.12. Lost to Follow Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (3 telephone calls and a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.13 Replacement of Subjects

Subjects in the dose-escalation phase who are not evaluable for DLT assessment will be replaced with another subject at the same dose level.

7.14 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the investigator. AEs will be followed up. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

7.15 Study Suspension or Termination

NeoImmuneTech reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects

- Subject enrollment is unsatisfactory
- Noncompliance that might significantly jeopardize the validity or integrity of the study

Enrollment into the study may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial to a given treatment.

8.0 STUDY TREATMENT

8.1. Study Treatment Administration

Reported AEs and potential risks are described in [Section 12.0](#). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Treatment will be administered in the hospital.

Table 2: Study treatment details

Study Treatment	Dosage Formulation	Unit Dose Strength	Dosage Level(s)	Route	Regimen or Treatment Day	Sourcing
Kymriah®	Suspension for intravenous infusion	0.6 to 6.0 x 10 ⁸ CAR-positive viable T cells/bag (ranges from 10-50mL)	N/A	Intravenous infusion	Day 0	Provided by SOC
Yescarta®	Suspension for intravenous infusion	2 × 10 ⁶ CAR-positive viable T cells per kg of body weight, with a maximum of 2 × 10 ⁸ CAR-positive viable T cells in approximately 68 mL.	N/A	Intravenous infusion	Day 0	Provided by SOC
Breyanzi®	Suspension for intravenous infusion	A single dose contains 50 to 110 × 10 ⁶ CAR-positive viable T cells with each component supplied separately in one to four single-dose vials	N/A	Intravenous infusion	Day 0	Provided by SOC
NT-17	Solution for injection	25 mg/1.0 mL	Dose in µg/kg ^a	Intramuscular injection	Day 21 (+/- 2 days)	Provided by Sponsor (NIT)

^aRefer to [Section 7.1](#) for assigned dose level.

8.2 Kymriah® 8.2.1 Description

Kymriah® is a CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for 4-1BB (CD137) and CD3 zeta (19).

Kymriah is prepared from the subject's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells, then transduced with the lentiviral vector containing the anti-CD19 CAR transgene, and activated with anti-CD3/CD28 antibody coated beads. The transduced T cells are expanded in cell culture, washed, and formulated into a suspension, which then is cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a subject-specific infusion bag(s). The product is thawed prior to infusion. The thawed product is a colorless to slightly yellow suspension of cells.

In addition to T cells, other cell populations, including monocytes, NK cells, and B cells, may be present. The formulation contains 31.25% (v/v) of Plasma-Lyte A, 31.25% (v/v) of 5% Dextrose/0.45% sodium chloride, 10 % Dextran 40 (LMD)/5% Dextrose, 20% (v/v) of 25% Human Serum Albumin (HSA), and 7.5% (v/v) Cryoserv® dimethylsulfoxide (DMSO) (19).

8.2.2 How Supplied / Storage and Handling / Dosage and Administration

Kymriah is acquired commercially for SoC CAR-T therapy, and should be supplied, stored, handled, and administered per approved labeling.

8.3 Yescarta®

8.3.1 Description

Yescarta is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare Yescarta, a patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded and infused back into the patient, where they can recognize and eliminate CD19-expressing target cells. Yescarta is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and activated with anti-CD3 antibody in the presence of IL-2, then transduced with the replication incompetent retroviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient specific infusion bag. The product is thawed prior to infusion. In addition to T cells, Yescarta may contain NK and NK-T cells. The formulation contains 5% dimethyl sulfoxide (DMSO) and 2.5% albumin (human).

8.3.2 How Supplied / Storage and Handling / Dosage and Administration

Yescarta is acquired commercially for SoC CAR-T therapy, and should be supplied, stored, handled, and administered per approved labeling.

8.4 Breyanzi®

8.4.1 Description

Breyanzi is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell

lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3b who have:

- refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
- refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
- relapsed or refractory disease after two or more lines of systemic therapy.

Limitations of use: Breyanzi is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma

8.4.2 How Supplied / Storage and Handling / Dosage and Administration

Breyanzi is acquired commercially for SoC CAR-T therapy, and should be supplied, stored, handled, and administered per approved labeling.

8.5 NT-I7

Product Name: NT-I7 (aka rhIL-7-hyFc, efineptakin alfa)

Chemical Name: NT-I7

Established Name: Recombinant human interleukin-7-hyFc

Chemical Formula: $C_{4012}H_{6350}N_{1104}O_{1238}S_{42}$

Structural Formula: NT-I7 is a fusion protein comprising human IL-7 fused to the human IgD hinge region. This in turn is fused to the N-terminal region of CH2 from IgD and two key regions of the antibody IgG4: C-terminal region of CH2 and the entire CH3 region.

8.5.1 NT-I7 Pharmaceutical Information

NT-I7 protein is produced by inserting the gene expressing rhIL-7-hyFc into the eukaryotic expression vector pAD15 at the Multiple Cloning Site. The CHO cell line DG44 is used to produce NT-I7. NT-I7 has a molecular weight of 104 KDa and is composed of 400 amino acids with 155 amino acids for IL-7 and 30 for the IgD hinge, 8 for IgD the CH2 domain, and 207 for the IgG4 region. NT-I7 contains 11 disulfide bonds, 1 O-glycosylation and 3 N-glycosylation sites.

8.5.2 Pharmaceutical Properties

NT-I7 is supplied in a sterile, preservative-free liquid form in a single-use vial. One vial (1.0 mL) contains 25 mg per 1.0 mL of the active ingredient of the finished drug product. The purity of the active ingredient must be 89.0% or higher based on size-exclusion ultra-high-performance liquid chromatography (SE-UHPLC) testing and 90.0% or higher based on reverse-phase high-performance liquid chromatography (RP-HPLC) testing. The NT-I7 finished drug product should be a colorless, clear solution and should not contain any particulate matter that can be observed visually.

8.5.3 Dosage Form

In addition to the active ingredient NT-I7, each vial contains sucrose, D-sorbitol, tri-sodium citrate dehydrates, citric acid monohydrate and Polysorbate 80 as a stabilizer and buffer. These ingredients meet the specification criteria of the European pharmacopeia (Ph. EUR). NT-I7 is supplied in a 1.0 mL vial package at a concentration of 25 mg protein/mL. The finished drug product solution contained in the vial is a liquid injection dosage form at pH 5.0 ± 0.5 and a colorless, clear solution. There should not be any floating particulates under gross observation. NT-I7 will be injected intramuscularly. Guidelines for IM injection by the research nurse or investigator are described in the Pharmacy Manual.

8.5.4 Storage and Handling of NT-I7

Vials that contain NT-I7 must be kept refrigerated at 2~8°C. NT-I7 vials should NEVER BE FROZEN. It is recommended that vials are protected from direct light until the time of use.

8.5.5 Assessment of Subjects prior to NT-I7 Dosing

Subjects will be hospitalized for NT-I7 injection and monitored for at least 24 hours after NT-I7 injection. If subjects develop Grade 2 or higher AEs, subjects will remain hospitalized until resolution of AEs to grade 1 or 0. Subjects can be kept in the hospital longer at the discretion of the treating physicians.

Check complete blood count (CBC) prior to NT-I7 injection. If platelet count $< 50,000/\mu\text{L}$, subject should receive platelet transfusion to increase platelet count to $> 50,000/\mu\text{L}$. Correction for other hematologic parameters, such as hemoglobin, should be done per standard of care.

8.5.6 Route of Administration

IM injection. Refer to the Pharmacy Manual for detailed instructions.

8.5.7 NT-I7 Dosing

Subjects will receive NT-I7 according to the following dose escalation schedule. Dose escalation will proceed within each dose level as described in [Section 7.1.1](#).

The NT-I7 dose will be administered 60 (± 10) minutes on scheduled days where administration is planned. NT-I7 dose administered will be determined using the subject's body weight.

NT-I7 will be injected intramuscularly. Guidelines for IM injection by the research nurse or investigator are described in the Pharmacy Manual.

8.5.8. Dose Calculations

The dose of NT-I7 administered should be determined using the subject's weight. Since each subject will receive only a single dose on Day 21, weight obtained on Day 21 should be used to calculate dose of NT-I7. Dosing is by actual body weight.

For obese subjects ($\text{BMI} \geq 30$), dosing will be determined by adjusted body weight. Proceed with the following steps:

1. Determine Ideal Weight (1 kg = 2.2 lbs):

Males: $50 \text{ kg} + 2.3 \text{ kg} \times (\text{inch over 5 feet})$

Females: $45.5 \text{ kg} + 2.3 \text{ kg} \times (\text{inch over 5 feet})$

(Subjects less than 5 feet: subtract 2.3 kg/inch under 5 feet)

2. Determine Adjusted Body Weight:

$\text{Ideal Weight} + 0.4 \times (\text{actual weight} - \text{ideal weight}) = \text{adjusted body weight}$

At higher dose levels, IM injection volumes $\geq 1 \text{ mL}$ may cause injection site pain. Distribution of injections across multiple IM sites will minimize the subject's discomfort related to IM injection. Dose volumes greater than 1 mL should be divided into 2 or more injections and the maximum volume administered in a single IM injection should be no greater than 1 mL. Please refer to the Pharmacy Manual for more detailed information.

Subjects will have their vital signs (heart rate, respiratory rate, blood pressure and temperature) determined within 60 minutes $\pm$ 10 minutes before the NT-I7 injection.

8.6 Discontinuation of Study Participation

An individual subject will be discontinued from study participation if any of the following occur in the subject in question:

- Confirmed progression of disease
- Withdrawal of consent from the study
- Lost to follow-up
- Initiation of alternative anticancer therapy including another investigational agent
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (e.g., refusal to adhere to scheduled visits)
- Pregnancy or intent to become pregnant
 - All women of child-bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
 - The investigator must immediately notify the Sponsor within 24 hours in the event of a confirmed pregnancy in a subject participating in the study.

Subjects who are permanently discontinued from study participation regardless of the reason (due to an AE, other), will be identified as having permanently discontinued study participation and will be followed for protocol-specified assessments (per the Follow-up Schedule of Assessments) including follow-up of any AEs unless consent is withdrawn specifically from further study participation; the subject is lost to follow-up; the subject starts alternative anticancer treatment; or the subject is enrolled in another clinical study. All subjects will be followed for survival every 90 days ($\pm$ 7 days) until death, lost to follow-up, withdrawal of consent or end of the study, whichever occurs first. Survival follow-up can be done either by in-person visit or by telephone assessment. Subjects who decline to return to the site for evaluations should be contacted by phone per the Follow-up Schedule of Assessments to assess for survival and subsequent anticancer treatment received unless consent is withdrawn.

9.0 STUDY PROCEDURES AND ASSESSMENTS

9.1 Study Procedures

Schedule of Assessments shows all procedures to be conducted at the screening visit, baseline treatment, on-treatment, end of treatment, and follow-up visits. Refer to Section 9.4.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last. The timing of the first 2 assessments should be such that it allows the blood draw (e.g., PK blood sample) to occur at the proper nominal time.

All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.

9.2 NT-I7 Pharmacokinetics (PK)

The pharmacokinetic (PK) profile of NT-I7 will be studied in all subjects. The quantification of NT-I7 in serum samples is based on an analytically validated method using an electrochemiluminescence sandwich immunoassay. Subject samples will be collected on Day 21- 0 hours (pre-dose), 2 and 6 hours (after NT-I7 administration), Day 22, Day 28, and Day 35 as indicated in [Table 3](#).

Note: The precise NT-I7 administration time and the precise PK draw time should be recorded accurately and prospectively to fully interpret these values.

Table 3: Pharmacokinetic timepoints (All subjects)

Treatment Cycle/Visit	Week 3				Week 4	Week 5
Scheduling Window	Day 21			Day 22	Day 28 ± 2 days	Day 35 ± 2 days
Hours	0 h	2 h (±15mins)	6 h (±30mins)	24 h (±1h)		
Pharmacokinetics*	X ^a	X ^b	X ^b	X ^b	X	X
^a To be collected prior to study agent(s) administration on a dosing day. ^b Blood draws are timed after NT-I7 administration is complete. [*] Details on blood collection, handling, and shipping are provided in the <i>Laboratory Manual</i> .						

9.3 Immunogenicity

Immunogenicity to NT-I7 will be measured using a risk-based, tiered testing approach. This includes a core assay comprising screening, confirmatory, and titer testing for detecting anti-drug antibodies (ADA) to NT-I7 as well as an IL-7 epitope-specific assay, and a cell-based neutralizing antibody assay for detecting anti-NT-I7 antibodies that may neutralize IL-7 bioactivity in patient serum samples. Subject samples will be obtained on Day 21 (pre-dose NT-I7), Day 35, Day 49, Day 63, and Day 100 administered to evaluate the prevalence and incidence of treatment-emergent/boosted ADA. All immunogenicity assays have been analytically validated.

9.4 Schedule of Assessments

Table 4: Schedule of Assessments

Phase 1b														
Treatment Week / Visit	Screening	SOC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-I7
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14 days	± 7 days
Lymphodepletion		X												
CD19 CAR T-cell infusion ¹⁷			X											
NT-I7							X							
Informed consent ¹	X													
Verify eligibility criteria	X						X							

Phase 1b														
Treatment Week / Visit	Screening	SOC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-17
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14 days	± 7 days
Prior cancer treatment and disease history including relapsed/refractory status ¹⁹	X													
Disease assessment by 2014 IWG Criteria for lymphoma and Whole body FDG-PET/CT scan		X						X					X	Per CAR-T SOC
Bone marrow biopsy and aspirate ²¹	X													
Physical exam	X	X		X	X	X	X	X	X	X	X	X	X	
Demographics	X													
Medical history	X													
ECOG performance status	X			X			X			X			X	

Phase 1b														
Treatment Week / Visit	Screening	SOC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-17
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14 days	± 7 days
Vital signs ³	X	X		X	X	X	X	X	X	X	X	X	X	
Height ⁴	X													
Weight	X	X		X	X	X	X	X	X	X	X	X	X	
AEs/SAEs Assessment ⁵	X	X		X	X	X	X	X	X	X	X	X	X	
Concomitant medications ²	X	X		X	X	X	X	X	X	X	X	X	X	X
12-lead ECG ⁶	X			X			X			X			X	
Cardiac Enzymes (Troponin (Tnl or TnT) and CK-MB) ⁶	X			X			X			X			X	
Echocardiogram ²²	X ²²			X ⁶			X ⁶			X ⁶			X ⁶	
Hematology ⁷	X	X		X	X	X	X	X	X	X	X		X	
Serum chemistry ⁸	X			X		X	X	X		X	X		X	

Phase 1b														
Treatment Week / Visit	Screening	SOC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-I7
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14 days	± 7 days
Coagulation parameters	X			X			X			X			X	
Thyroid Function Tests ⁹	X			X			X			X			X	
Urine or Serum Pregnancy Test ¹⁰	X			X			X			X			X	
Lymphocyte Subset Panel ¹⁸		X		X	X	X	X	X	X	X			X	
Urinalysis ¹¹	X			X		X	X	X		X	X		X	

Phase 1b														
Treatment Week / Visit	Screening	SOC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-17
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14 days	± 7 days
Fresh or archival biopsy (Fresh – optional) Archival – required if available ¹⁶	X													
Immunogenicity (NT-17 ADA)							X		X		X	X	X	
Pharmacokinetics ¹²	Refer to Table 3 for PK sampling													
Immunophenotyping ¹³		X		X	X	X	X	X	X	X			X	
FACS/PCR		X		X	X	X	X	X	X	X			X	
Serum cytokine profiling		X		X	X	X	X	X	X	X			X	
scRNA-seq						X			X				X	

Phase 1b														
Treatment Week / Visit	Screening	SOC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-I7
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14 days	± 7 days
Polyfunctional CAR-T cell, T cells		X				X			X				X	
MRD (Ig-HTS) ²⁰		X			X		X	X					X	

¹Written consent must be obtained prior to performing any protocol specified procedure.

²Prior medications – Record all medications (prescription and over-the-counter [OTC]) taken within 30 days of Screening visit. Concomitant medications – Enter all medications (prescription and OTC) taken between Consent through Day 100. Follow-up anti-cancer therapies should continue to be recorded during survival follow-up.

³Vitals (blood pressure, heart rate, respiratory rate, temperature) to be collected in a standardized manner in a sitting position after the subject has rested comfortably for ~5 minutes.

⁴Height is measured on the first visit during Screening only.

⁵Adverse event recording including immune related adverse events will commence from the time of consent through Day 100.

⁶Duplicate ECGs, at least 5 minutes apart, and serum cardiac enzyme levels (Troponin (TnI or TnT) and CK-MB) must be obtained at Screening, Days 1, 21, 42, and 100. Please refer to [Section 9.9.2](#) for guidance on handling clinically significant ECG and/or serum cardiac enzyme results.

⁷Hematology includes complete blood count (CBC) with differential, including but not limited to red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count with differential (neutrophil count including lymphocyte, monocyte, eosinophil, basophil counts and bands), absolute neutrophil count (ANC), and platelet count.

⁸Chemistry includes (but is not limited to) sodium, potassium, calcium, phosphorus, chloride, magnesium, bicarbonate, blood urea nitrogen (BUN) or urea, serum creatinine, glucose, uric acid, albumin, total protein, alkaline phosphatase, lactate dehydrogenase, bilirubin (indirect and direct), aspartate serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum pyruvic transaminase (ALT/SGPT).

⁹Thyroid function testing: thyroid-stimulating hormone (TSH), free Triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)

¹⁰Serum pregnancy test to be performed at the Screening visit for all females except those surgically sterile or 1 year postmenopausal. Subsequent serum or urine pregnancy tests could be performed as noted or per Investigator's discretion. A serum or urine pregnancy test must be performed within 72 hours of the first dose of NT-I7. Tests completed > 72 hours must be repeated prior to NT-I7 dosing.

¹¹Urinalysis (a urine dipstick may be used) at scheduled visits.

¹²For sampling details of PK, please refer to [Table 3](#). Additional information on handling and shipping are provided in the *Laboratory Manual*.

¹³Whole blood will be collected for the multispectral immunophenotyping to obtain absolute cell counts for CD4+ and CD8+ T-cell and other cell types as necessary.

¹⁴ SOC CD19 CAR T-cell infusion will be given within 2 to 11 days after lymphodepletion therapy. The day CAR T-cell therapy is given will be considered the Baseline Visit, Day 0. All baseline samples for correlative analyses will be collected on the Day 0 Baseline Visit.

¹⁵ End of Study Visit: Should the patient withdraw or be withdrawn from the study early, then all procedures and assessments should be completed in this column for the End of Study visit.

¹⁶ Tumor tissue should be tested per the site's local standard of care to confirm disease status, and this should be noted on the site's pathology report. It is recommended for the subject to have a biopsy at time of progression. Biopsy at CR is optional.

¹⁷ The date CAR-T Therapy cells were collected, number of cells collected, and number of cells infused should be documented on the CAR-T Therapy administration eCRF.

¹⁸ Lymphocyte panel to include: Absolute CD3+ cells, %CD3, Absolute CD4+ cells, %CD4, Absolute CD8+ cells, %CD8, CD4/CD8 ratio.

¹⁹ Cancer History to include documentation of double- or triple- hit, double- or triple- expressor, germ cell of origin, and International Prognostic Index (IPI) at enrollment.

²⁰ Minimum Residual Disease will be completed during the Dose Expansion only.

²¹ Screening bone marrow biopsy aspirate samples are required for submission in Dose Expansion for subjects with bone marrow involvement only. Prior bone marrow biopsy results should be updated into the EDC for those without bone marrow involvement. Bone marrow biopsy aspirate samples are not required for submission in Dose Escalation.

²² Echocardiogram is only performed at screening in cases of abnormal ECG or abnormal serum levels of cardiac enzymes where additional cardiac follow-up is needed to confirm eligibility.

9.5 Assessments

9.5.1 Anti-tumor activity/Efficacy

Disease assessments will be based on IWG response criteria for lymphoma [Lugano classification (3)] and will be performed according to the schedule of procedures presented in Section 9.4, and should not be shifted due to dosing delays. All subjects will be followed for survival according to the schedule of procedures through the end of the study (defined as 3 months after the final subject is enrolled or the sponsor stops the study, whichever occurs first).

Whole body FDG-PET/CT scans will be performed at Baseline, 1 month, 3 months, and at the time of achieving a CR. FDG-PET/CT scans- at additional time points are optional. CT scans can be used to assess anti-tumor activity at 6 months and 12 months post-CAR T-cell Therapy per SOC during survival follow-up. It is recommended that subjects who experience disease progression have a confirmatory FDG-PET/CT scan at Day 63 or 4 weeks after the initial positive scan to confirm true disease progression from pseudo-progression per the treating investigator's discretion. Once a subject enters the survival follow-up, imaging scans should follow standard-of-care guidelines for CAR-T cell therapy. If a scan is performed during the 90-day survival follow-up interval, it is recommended that the results be recorded on the applicable eCRF page.

In addition to imaging scans, tumor assessments should also include the following evaluations: physical examination (with photograph and measurement of skin lesions, as applicable, and spleen size documentation); bone marrow biopsy and aspirate at screening (per the schedule of procedures) and at the time of achieving CR for subjects with known bone marrow involvement.

9.6 Tumor Evaluations

9.6.1 Physical examination

- Lesions detected by physical examination will only be considered measurable if superficial, e.g., skin nodules, and palpable lymph nodes and spleen. Documentation by color photography including ruler is recommended for estimating the size of skin lesions.

9.6.2 Imaging

FDG-PET/CT scans should be performed at Baseline, 1 month, and 3 months and at the time of achieving a CR. FDG-PET/CT at other timepoints are optional.

- CT scan can be used to assess anti-tumor activity at 6 months and 12 months post-CAR T-cell Therapy per SOC during survival follow-up, with the same guidelines as indicated below.

9.6.3 Measurability of Tumor Lesions

Up to 6 of the largest nodes, nodal masses, or other lymphomatous lesions that are measurable in 2 diameters (longest diameter [LDi], shortest diameter, and longest perpendicular diameter to

LDi) and are representative of the subject's disease should be selected. Tumor lesions will be categorized as follows:

- **Measurable Node** – Must have an LDi > 1.5 cm
- **Measurable Extranodal Disease** (e.g., hepatic nodules) – Should have an LDi > 1.0 cm
- **Non-measured Disease** (e.g., cutaneous, gastrointestinal, bone, spleen, liver, kidney, pleural or pericardial effusions, and ascites) – All lesions that do not meet the criteria for nodal or extranodal disease

9.6.4 Evaluation of Response

Response will be assessed based on IWG response criteria for lymphoma (Lugano classification (3); [Table 5: Response Assessment by IWG Response Criteria for Lymphoma](#)).

Table 5: Response Assessment by IWG Response Criteria for Lymphoma

Response and Site	PET-CT Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	• Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites

Response and Site	PET-CT Based Response	CT-Based Response
	- At interim, these findings suggest responding disease - At end of treatment, these findings indicate residual disease	- When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value - When no longer visible, 0 x 0 mm - For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/ nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive Disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/ nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and

Response and Site	PET-CT Based Response	CT-Based Response
		• Increase by > 50% from PPD nadir and • An increase in LDi or SDi from nadir • 0.5 cm for lesions $\leq$ 2 cm • 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement
Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions. *A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors). †PET 5PS: 1, no uptake above background; 2, uptake $\leq$ mediastinum; 3, uptake > mediastinum but $\leq$ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.		

9.6.5 Appearance of New Lesions

If a new lesion is equivocal (e.g., because of its small size), follow-up evaluation will clarify if it truly represents new disease. If repeat scans confirm there is a new lesion, then progression should be declared using the date of the initial scan. The appearance of new lesions is considered PD according to IWG response criteria for lymphoma. Considering the unique response kinetics observed with immunotherapy, new lesions may not represent true PD.

9.7 Pseudo-Progression after CAR-T Treatment

Pseudo-progression has been observed in multiple B cell lymphoma patients after receiving CAR T cell therapy. (33-36) Timing of pseudo-progression is early. Symptoms are usually seen around day 5 post-CAR-T infusion, with scans showing increased tumor mass about 1-2 weeks post-infusion. Pseudo-progression is usually accompanied with worsening or new symptoms with CRS and/or neurological toxicities co-occurring.

New lesion or site involvement has been observed in scan during pseudo-progression.(35, 37) IL-8 may be an informative biomarker to distinguish pseudo-progression from true progression, as has been suggested in tumor patients receiving immunotherapy.(33) Since we hypothesize that NT-I7 will boost CAR T-cell numbers, it is reasonable to consider rapid progression as possible pseudo-progression.

9.8 Biopsies

Tumor tissue will be evaluated. The biopsy sample must be from the tumor; bone marrow samples are not acceptable in lieu of tumor tissue. LBCL type must be clearly noted on the pathology report. Other biomarkers may be evaluated as determined by additional data.

Details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual. Tumor biopsies will be stored at an appropriate vendor selected by NIT and may undergo centralized pathology review at discretion of the sponsor.

9.8.1 Fresh Tumor Biopsy

Tumor biopsy and/or archival tissue are not required in Dose Escalation. In Dose Expansion, should a subject not have archival tumor tissue available, then the subject may agree to an optional fresh tumor biopsy collected from a safely accessible site as deemed per the site PI. Subjects that do not have a safely accessible area to biopsy for the fresh tumor requirement will not be excluded from the study.

Biopsies should be obtained from safely accessible sites (as determined by the investigator) using low-risk procedures. Subjects may consent to optional biopsies as follows:

- At screening, when archival tumor tissue is not available
- At complete response
- At the time of progression

9.8.2 Archival Tumor Sample

Archival tumor tissue is required from all subjects (if available) and should be provided per the schedule of procedures. Archival tumor samples should be prepared as stated in the Lab Manual.

9.9 Medical History, Physical Examination, Electrocardiogram, and Vital Signs

9.9.1 Medical History and Physical Examination

Physical examinations will be performed according to institutional guidelines on study days noted in Section 9.4 and will include assessments of the head, eyes, ears, nose, and throat, respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems; weight; and height (at screening only). Bidimensional measurement of liver and spleen by palpation will be performed. In addition, symptoms of fever, night sweats, and weight loss should be documented.

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre- study grade or below.

Physical examinations must be complete or may be focused physical examinations as clinically indicated based on symptoms and signs or as indicated by the investigator. If the subject has completed a physical examination within 72 hours before Day 1, it will not need to be repeated unless clinically indicated.

9.9.2 Electrocardiograms

ECGs (12-lead) will be recorded on study days. ECGs should be performed after the subject has been resting for 5 minutes in a recumbent or semi-recumbent position. Duplicate ECGs obtained 5 minutes apart must be obtained on study visit days requiring ECGs.

For patients with recent clinically significant cardiac disease (within one year): ECG and serum cardiac enzyme levels (see [Section 9.13](#)) are evaluated at screening and followup. If ECG or serum cardiac enzyme levels are found to be clinically significant at screening, an echocardiogram must be performed and the patient must be assessed by a local cardiologist to confirm that the subject does not have unstable cardiac disease and ensure he or she meets the cardiac eligibility requirements to be included in the trial.

If upon followup visits, the ECG, serum cardiac enzyme levels ([Section 9.13](#)), and echocardiogram have not changed from screening, further clearance by a cardiologist is not required for continuation on study. However, if the ECG, serum cardiac enzyme levels, or echocardiogram worsen at followup compared to baseline, another evaluation with a cardiologist will be required.

For patients with remote (>1 year) or no history of cardiac disease: ECG and serum cardiac enzyme levels are evaluated at screening. If clinically significant, echocardiogram will be performed at screening and subsequent followup visits. Clearance by the PI will be acceptable in cases of clinically significant ECG, serum cardiac enzyme levels, or echocardiogram.

In case of clinically significant ECG abnormalities, including an ECG that demonstrates a QT corrected using Fridericia's formula (QTcF) value > 500 milliseconds, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation.

The following variables will be reported: heart rate, PR, QRS, and QT intervals from the primary lead of the digital 12-lead ECG.

9.9.3 ECOG Performance Status

Performance status as determined by the ECOG scale (38) (will be recorded in the electronic case report form (eCRF) per the schedule in Section 9.4.

Table 6: Eastern Cooperative Oncology Group Performance Status	
Grade	Performance Status Criteria
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

9.10 Vital Signs

Vital signs (temperature, blood pressure [BP], pulse rate, and respiratory rate) will be measured at each study visit through the safety follow-up. It is recommended that vitals be done using the same method and in the same position throughout the study.

9.11 Safety

Toxicity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Exception: CRS and ICANS will be graded using ASTCT guidelines.

- Safety analysis will be conducted on all subjects who receive NT-I7 injection and will include the frequency of all AEs and laboratory abnormalities.

Additional safety assessments will include physical examination; medical history; ECG; performance status; weight; vital signs measurements; clinical laboratory testing (hematology, clinical chemistry, and urinalysis).

Safety assessments will be performed as per the Schedule of Assessments. Safety assessment may be performed at additional time points during the study at the discretion of the Investigator in the interest of subject safety.

9.12 Adverse Events

AEs will be followed, recorded, and reported in line with the procedures described in [Section 12](#).

9.13 Laboratory Evaluations

Correlative labs, including PK and ADA/nAb assessments, will be performed by either a central laboratory or a third-party vendor selected and reviewed by NIT. All other laboratory assessments will be performed at local laboratories. Blood and urine samples will be collected at the times indicated in the Schedule of Assessments. On D21 (+/- 2 days), when NT-I7 will be administered, clinical laboratory parameters are required to be performed *before* the administration of NT-I7.

The following parameters will be assessed:

Hematology: hemoglobin, hematocrit, red blood cells, platelets, total white blood cell (WBC) count, differential WBC count, and absolute neutrophil count

Biochemistry: Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST, ALT, LDH, uric acid, Troponin (TnI or TnT) and CK-MB

Urinalysis: pH, specific gravity, creatinine, glucose, bilirubin, blood, and protein

Coagulation: PT/INR

Lymphocyte panel: Absolute CD3+ cells, %CD3, Absolute CD4+ cells, %CD4, Absolute CD8+ cells, %CD8, CD4/CD8 ratio

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during the patient's participation in the study should be repeated until the values return to normal, or baseline, or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, then the etiology should be identified, and the Study's Medical Monitor and the Sponsor notified.

A patient should be cleared by the investigator or a local cardiologist if the serum cardiac enzyme level (Troponin (TnI or TnT) and CK-MB) is clinically significant (through send-out testing if needed). See [Section 9.9.2](#) for details.

10.0 MANAGEMENT OF ADVERSE EVENTS

The National Cancer Institute (NCI) CTCAE Version 5.0 will be used to grade AEs, except CRS and ICANS which will be graded using ASTCT guidelines. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in this section.

Subjects will be evaluated for AEs (all grades) at each study visit for the duration of their participation in the study.

10.1 Kymriah®

Because of the risk of Cytokine Release Syndrome (CRS) and neurological toxicities, Kymriah is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAHS REMS. The required components of the KYMRIAHS REMS are:

- Healthcare facilities that dispense and administer Kymriah must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each subject for administration within 2 hours after Kymriah infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer Kymriah are trained about the management of CRS and neurological toxicities (19).

10.1.1 Management of Severe Adverse Reactions

The following guidance is taken from the Kymriah Prescribing Information, revised May 2022 (19).

10.1.1.1 Cytokine Release Syndrome

Identify cytokine release syndrome (CRS) based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 7 (19). Alternative CRS management strategies may be implemented based on appropriate institutional or academic guidelines.

Table 7: CRS Grading and Management Guidance

CRS Grade ^a	Symptomatic treatment	Tocilizumab	Corticosteroids
Grade 1 Mild symptoms requiring	Exclude other causes (e.g., infection) and treat specific symptoms (e.g., with	In patients with persistent (> 3	Not applicable

CRS Grade^a	Symptomatic treatment	Tocilizumab	Corticosteroids
symptomatic treatment only (e.g., low grade fever, fatigue, anorexia, etc.)	antipyretics, antiemetics, analgesics, etc.)	days) or refractory fever, consider managing as Grade 2 CRS ^b .	
Grade 2 Symptoms require and respond to moderate intervention Oxygen requirement < 40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity	Antipyretics, oxygen, intravenous fluids and/or low dose vasopressors as needed.	Administer tocilizumab ^c intravenously over 1 hour: - 8 mg/kg (max. 800 mg) if body weight ≥ 30 kg - 12 mg/kg if body weight <30 kg If no improvement after first dose, repeat every 8 hours (limit to a maximum of 3 dosages in 24 hours period; maximum total of 4 doses).	If no improvement within 24 hours of tocilizumab, administer a daily dose of 2 mg/kg/day methylprednisolone intravenously (or equivalent) until vasopressor and oxygen no longer needed, then taper. If not improving, manage as appropriate grade below.
Grade 3 Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis	High-flow oxygen Intravenous fluids, and high-dose or multiple vasopressors Treat other organ toxicities as per local guidelines.	Per Grade 2 If not improving, consider alternative therapy ^d .	Per Grade 2 If not improving, manage as Grade 4.
Grade 4 Life-threatening symptoms	Mechanical ventilation	Per Grade 2	Administer methylprednisolone 1,000 mg

CRS Grade ^a	Symptomatic treatment	Tocilizumab	Corticosteroids
Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)	Intravenous fluids and high-dose vasopressor(s) Treat other organ toxicities as per local guidelines.	If not improving, consider alternative therapy ^d .	intravenously one to two times per day for 3 days. If not improving, consider methylprednisolone 1,000 mg intravenously two to three times a day or alternate therapy ^d . Continue corticosteroids until improvement to Grade 1, and then taper as clinically appropriate.
^a Lee et al. 2014. ^b Santomasso et al. 2021. ^c Refer to tocilizumab Prescribing Information for details. ^d Alternative therapy includes anti-cytokine and anti-T cell therapies as per institutional policy and published guidelines such as (but not limited to) anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.			

10.1.1.2 Neurologic Toxicities

Patients should be monitored for neurologic toxicities, including ICANS, following KYMRIA[®] infusion, particularly during and after resolution of CRS. Identify neurologic toxicities based on clinical presentation. Evaluate for and treat other causes of neurological symptoms. Consider non-sedating seizure prophylaxis (e.g., levetiracetam) for patients at higher risk of seizure, such as those with seizure history, CNS disease, concerning EEG findings, or neoplastic brain lesions. If neurologic toxicity is suspected, manage according to the recommendations in [Table 8](#). Alternative neurologic toxicities management strategies may be implemented based on appropriate institutional, academic, or consensus guidelines.

Table 8: Guidance for Grading and Management of ICANS

ICANS Grade ^a	No concurrent CRS	Concurrent CRS
Grade 1 ICE score ^b : 7-9 with no depressed level of consciousness	Offer supportive care with intravenous hydration and aspiration precautions.	Administer tocilizumab at any grade CRS, as per dosage recommendation in Table 7 .

ICANS Grade ^a	No concurrent CRS	Concurrent CRS
		Caution with repeated tocilizumab doses in patients with ICANS. Consider adding corticosteroids to tocilizumab past the first dose ^c .
Grade 2 ICE score ^b : 3-6 and/or Mild somnolence awaking to voice	Supportive care as above. Consider dexamethasone 10 mg intravenously every 6-12 hours or methylprednisolone equivalent (1 mg/kg intravenously every 12 hours) until the event is Grade 1 or less. If improving, taper corticosteroids.	Administer tocilizumab at any grade CRS, as per dosage recommendation in Table 7 . If refractory to tocilizumab past the first dose, administer dexamethasone 10 mg intravenously every 6-12 hours or methylprednisolone equivalent (1 mg/kg intravenously every 12 hours) until the event is Grade 1 or less, then taper corticosteroids.
Grade 3 ICE score ^b : 0-2* and/or Depressed level of consciousness awakening only to tactile stimulus and/or Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention and/or Focal or local edema on neuroimaging	Administer dexamethasone 10 mg intravenously every 6-12 hours or methylprednisolone equivalent (1 mg/kg intravenously every 12 hours)	Administer tocilizumab at any grade CRS, as per dosage recommendation in Table 7 . Administer dexamethasone 10 mg intravenously every 6-12 hours or methylprednisolone equivalent (1 mg/kg intravenously every 12 hours). Continue corticosteroids until the event is Grade 1 or less, then taper corticosteroids. If not improving, manage as Grade 4.
Grade 4 ICE score ^b : 0* (patient is unarousable and unable to perform ICE)	Consider mechanical ventilation for airway protection. Administer high-dose methylprednisolone	Administer tocilizumab at any grade CRS, as per dosage recommendation in Table 7 . Administer methylprednisolone 1,000 mg

ICANS Grade ^a	No concurrent CRS	Concurrent CRS
and/or Stupor or coma and/or Life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between and/or Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, cranial nerve VI palsy, or Cushing's triad	intravenously 1,000 mg one to two times per day for 3 days. If not improving, consider 1,000 mg of methylprednisolone two to three times per day or alternate therapy ^d . Continue corticosteroids until improvement to Grade 1, and then taper as clinically appropriate. Treat seizures, status epilepticus, and cerebral edema as per institutional guidelines.	intravenously one to two times per day for 3 days. If not improving, consider methylprednisolone 1,000 mg intravenously two to three times per day or alternate therapy ^d . Continue corticosteroids until improvement to Grade 1, and then taper as clinically appropriate. Treat seizures, status epilepticus, and cerebral edema as per institutional guidelines.
^a ASTCT criteria for grading NT (Lee et al. 2019); NCI CTCAE criteria for grading NT used in clinical trials. ^b ICE Assessment Tool: (1) Orientation: orientation to year, month, city, and hospital: 4 points. (2) Naming: ability to name three objects (e.g., point to clock, pen, and button): 3 points. (3) Following commands: ability to follow simple commands (e.g., show me 2 fingers or close your eyes and stick out your tongue): 1 point. (4) Writing: ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point. (5) Attention: ability to count backward from 100 by 10: 1 point. ^c Santomasso et. al. 2021. ^d Alternate therapy may include anakinra, siltuximab, ruxolitinib, cyclophosphamide, antithymocyte globulin, or intrathecal hydrocortisone (50 mg) plus methotrexate (12 mg). * A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.		

10.2 Yescarta®

Because of the risk of CRS and neurologic toxicities, Yescarta is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS Program. The required components of the YESCARTA and TECARTUS REMS Program are:

- Healthcare facilities that dispense and administer Yescarta must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after Yescarta infusion, if needed for treatment of CRS.

- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

10.2.1 Management of Severe Adverse Reactions

The following guidance is taken from the Yescarta Prescribing Information, revised November 2022 (18).

Identify cytokine release syndrome (CRS) based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in [Table 9: CRS Grading and Management Guidance](#).

Table 9: CRS Grading and Management Guidance

CRS Grade	Tocilizumab	Corticosteroids
Grade 1: Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	• If symptoms (e.g., fever) not improving after 24 hours, consider managing as Grade 2.	• If not improving after 3 days, administer one dose of dexamethasone 10 mg intravenously.
Grade 2: Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO ₂ or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity. ^b	• Administer tocilizumab^c 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). • If no clinical improvement in the signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours as needed. • Limit to a maximum of 3 doses in a 24- hour period; maximum total of 4 doses. • If improving, discontinue tocilizumab.	• Administer dexamethasone 10 mg intravenously once daily. • If improving, manage as Grade 1 above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. • If not improving, manage as appropriate grade below.
Grade 3: Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO ₂ or hypotension requiring high-dose or multiple vasopressors or	• Per Grade 2. If improving, manage as appropriate grade above.	• Dexamethasone 10 mg intravenously three times a day. • If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less,

CRS Grade	Tocilizumab	Corticosteroids
Grade 3 organ toxicity or Grade 4 transaminitis.		then quickly taper as clinically appropriate. If not improving, manage as Grade 4.
Grade 4: Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2. If improving, manage as appropriate grade above.	- Administer methylprednisolone 1000 mg intravenously once per day for 3 days. - If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. - If not improving, consider methylprednisolone 1000 mg 2-3 times a day or alternate therapy.^d

a. Lee et al. 2014.

b. Refer to Table 11 for management of neurologic toxicity.

c. Refer to tocilizumab Prescribing Information for details.

d. Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.

10.2.1.1 Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicity/immune effector cell-associated neurotoxicity syndrome (ICANS). If ICANS is suspected, manage according to the recommendations in [Table 10: Neurologic Toxicity/ICANS Grading and Management Guidance](#). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities/ICANS should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Consider levetiracetam for seizure prophylaxis for any grade of neurologic toxicities.

Table 10: Neurologic Toxicity/ICANS Grading and Management Guidance

Grading Assessment ^a	Concurrent CRS	No Concurrent CRS
Grade 1	- Administer tocilizumab per Table 9 for management of Grade 1 CRS. - In addition, administer one dose of dexamethasone 10 mg intravenously. - If not improving after 2 days, repeat dexamethasone 10 mg intravenously.	- Administer one dose of dexamethasone 10 mg intravenously. - If not improving after 2 days, repeat dexamethasone 10 mg intravenously.
	Consider levetiracetam for seizure prophylaxis.	

Grading Assessment ^a	Concurrent CRS	No Concurrent CRS
Grade 2	- Administer tocilizumab per Table 9 for management of Grade 2 CRS. - In addition, administer dexamethasone 10 mg intravenously four times a day. - If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. - If not improving, manage as appropriate grade below.	- Administer dexamethasone 10 mg intravenously four times a day. - If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. - If not improving, manage as appropriate grade below.
	Consider levetiracetam for seizure prophylaxis.	
Grade 3	- Administer tocilizumab per Table 9 for management of Grade 2 CRS. - In addition, administer methylprednisolone 1000 mg intravenously once daily. - If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. - If not improving, manage as Grade 4.	- Administer methylprednisolone 1000 mg intravenously once daily. - If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. - If not improving, manage as Grade 4.
	Consider levetiracetam for seizure prophylaxis.	
Grade 4	- Administer tocilizumab per Table 9 for management of Grade 2 CRS. - In addition, administer methylprednisolone 1000 mg intravenously twice per day. - If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. - If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.^b	- Administer methylprednisolone 1000 mg intravenously twice per day. - If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. - If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.^b
	Consider levetiracetam for seizure prophylaxis.	

a. Severity based on Common Terminology Criteria for Adverse Events.

b. Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.

10.3 Breyanzi

10.3.1 Management of Severe Adverse Reactions

The following guidance is taken from the Breyanzi prescribing information, revised June 2023 (17).

10.3.1.1 Cytokine Release Syndrome

Identify cytokine release syndrome (CRS) based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table . Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

If concurrent neurologic toxicity is suspected during CRS, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in [Table 11](#) and [Table 12](#)
- Tocilizumab according to the CRS grade in [Table 11](#)
- Antiseizure medication according to the neurologic toxicity in [Table 12](#)

Table 11: CRS Grading and Management Guidance

CRS Grade ^(a)	Tocilizumab	Corticosteroids ^(b)
Grade 1 Fever	If less than 72 hours after infusion, consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). If 72 hours or more after infusion, treat symptomatically.	If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 24 hours. If 72 hours or more after infusion, treat symptomatically.
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO ₂ , or hypotension responsive to fluids or low	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen.	If less than 72 hours after infusion, administer dexamethasone 10 mg IV every 12-24 hours. If 72 hours or more after infusion, consider dexamethasone 10 mg IV every 12-24 hours.

CRS Grade ^(a)	Tocilizumab	Corticosteroids ^(b)
dose of one vasopressor, or Grade 2 organ toxicity.	Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (10-20 mg IV every 6 to 12 hours).	
	If no improvement or continued rapid progression, maximize dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.	
Grade 3	Per Grade 2.	Administer dexamethasone 10mg IV every 12 hours.
Symptoms require and respond to aggressive intervention.	If no improvement within 24 hours or rapid progression of CRS, repeat tocilizumab and escalate dose and frequency of dexamethasone (10-20 mg IV every 6 to 12 hours).	
Oxygen requirement greater than or equal to 40% FiO2, or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity, or Grade 4 transaminitis.	If no improvement or continued rapid progression, maximize dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.	
Grade 4	Per Grade 2	Administer dexamethasone 20 mg IV every 6 hours.
Life-threatening symptoms	If no improvement within 24 hours or rapid progression of CRS, escalate tocilizumab and corticosteroid use. If no improvement or continued rapid progression, maximize dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.	
Requirements for ventilator support or continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).		
(a.) Lee criteria for grading CRS (Lee et al, 2014).		
(b.) If corticosteroids are initiated, continue corticosteroids for at least 3 doses or until complete resolution of symptoms, and consider corticosteroid taper.		

10.3.1.2 Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicities ([Table 12](#)). Rule out other causes of neurologic symptoms. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. If neurologic toxicity is suspected, manage according to the recommendations in [Table 12](#).

If concurrent CRS is suspected during neurologic toxicity, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in [Table 11](#) and [Table 12](#)
- Tocilizumab according to the CRS grade in [Table 11](#)
- Antiseizure medication according to the neurologic toxicity in [Table 12](#)

Table 12: Neurologic Toxicity (NT) Grading and Management Guidance

NT Grade ^(a)	Corticosteroids and Antiseizure Medication
Grade 1	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.
Grade 2	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 mg IV every 12 hours for 2-3 days, or longer for persistent symptoms. Consider taper for a total steroid exposure of greater than 3 days. If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to a maximum of 20 mg IV every 6 hours. If no improvement after another 24 hours, rapidly progressing symptoms, or life-threatening complications arise, give methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided 4 times a day; taper within 7 days).
Grade 3	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 to 20 mg IV every 8 to 12 hours. Steroids are not recommended for isolated Grade 3 headaches.

NT Grade ^(a)	Corticosteroids and Antiseizure Medication
	If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (dose and frequency as per Grade 2). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 g/m².
Grade 4	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (dose and frequency as per Grade 2). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m².
(a.) NCI CTCAE criteria for grading neurologic toxicities, version 4.03.	

10.4 NT-I7

Clinical experience has demonstrated that development of autoimmune inflammatory conditions is a general risk with therapeutics intended to enhance anti-tumor T-cell responses. Such irAEs have been described for virtually all organ systems and include, but are not limited to: colitis, hepatitis, pneumonitis, endocrinopathy, ocular toxicity, pancreatic toxicity, myocarditis, and rash.

Risks of autoimmunity associated with NT-I7 are theoretical and yet not fully evaluated in the clinical setting. Due to this potential risk of NT-I7 to induce autoimmune conditions, subjects with a history of autoimmune disease will be excluded from this study.

None of the irAEs were reported in previous clinical studies with rhIL-7, or with NT-I7 monotherapy including the FIH study completed in normal healthy individuals, and solid tumor subjects (Study No. GX-I7-HV-001 and Study No. GX-I7-CA-003). However, two cases of fatal myocarditis were reported in the combination therapies with a checkpoint inhibitor, pembrolizumab and atezolizumab (Study No. NIT-110 and Study No. NIT-119).

Given the limited clinical experience with NT-I7, immune-related toxicities associated or possibly associated with NT-I7 should be closely monitored and carefully managed according to standard medical practice (e.g., thyroid hormone replacement for autoimmune hypothyroidism). Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology. In addition, ECG and serum cardiac enzyme levels will be tested to evaluate for cardiac toxicity. Although most irAEs observed with immune modulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (14). Discontinuation of NT-I7 may not have an immediate therapeutic effect, and there is no available antidote for NT-I7. The primary approach to mild irAEs (Grades 1–2) is supportive and symptomatic care. In severe cases, irAEs may be acutely managed with systemic corticosteroids, mycophenolate or TNF- α antagonists (1, 13, 14, 26, 39-53).

11.0 CONCOMITANT THERAPY

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study participation or vaccination may be required. Antimicrobial prophylaxis is permitted per institutional guideline and/or ASTCT guideline. The investigator should discuss any questions regarding this with the Sponsor or Sponsor's assigned designee. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study treatment requires the mutual agreement of the investigator, the Sponsor and the subject.

Any concomitant medications, including herbal preparations, taken during the study will be recorded in the eCRF. Concomitant medications should be collected from consent through Day 100. Anti-cancer therapies will continue to be documented during survival follow-up.

11.1 Prohibited Medications/Treatment

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The sponsor must be notified if a subject receives any of these during the study.

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than NT-I7
- Radiation therapy

Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Note: Inhaled steroids are allowed for management of asthma.

Note: Topical corticosteroids to treat injection site reaction are allowed.

- Immunostimulatory and immunosuppressive agents are prohibited.
- No data exist regarding the interaction of NT-I7 with commonly used herbal or non-traditional medications. Subjects should be instructed not to use such medications while receiving NT-I7 post-CD-19 CAR T-cell therapy.

Subjects who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

11.2 Medications Used with Caution

Investigators may prescribe concomitant medications or treatments (eg, acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed in [Section 11.1](#). Best supportive care (including antibiotics, nutritional support, colony stimulating factors, correction of metabolic disorders, optimal symptom control and pain management [including palliative radiotherapy, etc]) should be used when necessary for all subjects. Opioids can be used but with caution and under medical control after discussion with the medical monitor.

No data exist regarding the interaction of NT-I7 with drugs known to prolong the QT/QTc interval. Accordingly, subjects receiving these drugs while receiving NT-I7 post-CD19 CAR T-cell therapy should be closely monitored.

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

Concomitant medications should be collected from consent through the Day 100/ EOS visit. Concomitant medications should continue to be recorded in subjects withdrawn from trial for 30 days after NT-I7 injection. Concomitant medications administered 30 days after NT-I7 injection should be recorded for SAEs and adverse events of special interest (AESIs) as defined in [Section 12.4](#).

11.3 Rescue Medication & Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

12.0 ADVERSE EVENTS: ASSESSING AND REPORTING REQUIREMENTS

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study product is also an AE.

All AEs that occur on study, from the time the consent is signed to Day 100, must be reported. The reporting timeframe for AEs meeting the criteria of SAE is described in [Section 12.3](#).

AEs are reported in a routine manner during the study using the EDC system. Additionally, certain AEs must be reported in an expedited manner for timelier monitoring of subject safety and care. The following list of AEs (Sections [12.1](#) and [12.4](#)) and the characteristics of an observed AE will determine whether the event requires expedited reporting to the Sponsor or designee.

Electronic monitoring of AEs will be done through the EDC system and/or via email reporting by each clinical site to the Sponsor and/or Sponsor's safety designee. Per GCP, all sites must enter data in a timely manner. AEs meeting the criteria of SAE in the EDC system will trigger immediate review and distribution as needed and required by regulatory authorities.

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs at the time points specified and more frequently if clinically indicated.

12.1 Adverse Events and Potential Risks List

For lists of adverse reactions to Kymriah, Yescarta or Breyanzi, please refer to the current FDA-approved labeling.

For details on adverse reactions for NT-I7, please refer to Section [12.4](#) and the NT-I7 Investigator Brochure. Note: NT-I7 in combination with or following other agents could cause an exacerbation of any AE currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

12.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the CTCAE version 5.0 will be utilized for AE reporting, except CRS and ICANS which will be graded using ASTCT guidelines. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Grading for CRS and ICANS will follow ASTCT guidelines. Practice guidelines can be accessed via ASTCT website at <https://www.astct.org/learn/practice-guidelines>

Attribution of the AE will be graded as follows:

- Definite – The AE is *clearly related* to the study treatment.
- Probable – The AE is *likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE is *doubtfully related* to the study treatment.
- Unrelated – The AE is *clearly NOT related* to the study treatment.

12.3 Expedited Adverse Event Reporting

AE, SAEs, and other reportable safety events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up of AE, SAEs and other reportable safety events for outcome.

Expedited AE reporting for this study must be done by notifying the Sponsor and/or Sponsor's safety designee **within 24 hours** of the investigator or investigator designee knowledge of the event via the study EDC system and email <mailto:saereporting@amarexcro.com> and NIT112Safety@neoimmunetech.com as stipulated.

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to the Sponsor designated CRO, Amarex by telephone at 240-454-6844, fax: 240454-6602. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into the data capture system by the original submitter at the site.

12.3.1 Time Period and Frequency for Collecting AE, SAE, AESI and Other Reportable Safety Event Information

- All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment /allocation must be reported by the investigator.
- If subject withdraws early from the trial, all AEs or AESIs/irAEs from the time of treatment/ allocation through 30 days following cessation of study treatment must be reported by the investigator.
- All SAEs from the time of treatment/ allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment/ allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to have an attribution of possible, probable, or definitely related to NT-I7.

12.3.2 Expedited Reporting Guidelines

Use the study protocol number and the protocol-specific subject ID assigned during study registration on all reports. Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Note: A death occurring within 90 days of the last administration of study agent requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to PD should be reported as Grade 5 “Malignant neoplasm progression” to be coded under the system organ class (SOC) of “Neoplasms benign, malignant and unspecified (incl cysts and polyps). Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Table 13: FDA Reporting Requirements for Serious Adverse Events

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators must immediately (within 24 hours) report ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 Code of Federal Regulations [CFR] 312.64)

An AE is considered serious if it results in any of the following outcomes:

- 1) Death
- 2) A life-threatening AE
- 3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Abbreviations: AE=adverse event; CFR=Code of Federal Regulations; FDA=Food and Drug Administration; ICH=International Council for Harmonization; IME=important medical events; NIT=NeoImmuneTech.

12.4 Adverse Events of Special Interest for NT-I7

The following AEs are of special interest in subjects receiving NT-I7, as defined below and must be reported by the investigator expeditiously to the Sponsor and/or Sponsor’s Safety designee irrespective of regulatory seriousness criteria and the relatedness to the NT-I7. Immune-related adverse event (irAE) is defined as an AE associated with drug exposure that is consistent with an immune-mediated mechanism of action when there is no clear alternate etiology. For events which are potentially immune-related, additional information such as serologic, immunologic, and

histologic (biopsy) data and use of steroids or immunosuppressants will be used to support an irAE diagnosis.

- Potential drug-induced liver injury that includes an elevated ALT or AST $\geq 3 \times$ ULN in combination with an elevated bilirubin $\geq 2 \times$ ULN and, at the same time, an alkaline phosphatase (ALP) $< 2 \times$ ULN; no other reason can be found to explain the combination of increased AST or ALT, and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury. (54)
- Conditions (regardless of grade) suggestive of an autoimmune disorder, including but not limited to hepatitis, pneumonitis, colitis, pancreatitis, endocrinopathies (including but not limited to thyroiditis, Type 1 diabetes mellitus, adrenal insufficiency), myocarditis, myositis/polymyositis, rheumatoid arthritis, vasculitis, neuritis, systemic lupus erythematosus, Sjogren's syndrome, neuropathy/neuromuscular toxicity (Guillain-Barre syndrome and myasthenia gravis)
- Symptoms and signs suggestive of hypersensitivity, cytokine release, or infusion reaction syndromes with a different underlying pharmacological etiology
- Grade ≥ 2 diarrhea
- Grade ≥ 2 AST/ALT and Grade ≥ 2 total bilirubin elevation with constitutional symptoms
- Grade ≥ 3 hypoxia or dyspnea
- Grade ≥ 2 pleural effusion that is not due to the underlying disease (e.g., non-malignant pleural effusion)

12.5 Other Events Requiring Immediate Reporting

12.5.1 Overdose

For this study, an overdose of NT-I7 will be defined as any dose $> 1440 \mu\text{g/kg}$.

- An overdose with associated AEs is recorded as the AE on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

No specific information is available on the treatment of overdose of NT-I7. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

12.5.2 Pregnancy

If pregnancy occurs in a female subject who has received investigational product, the investigator or other site personnel informs the appropriate sponsor representative(s) ***within 24 hours of becoming aware of the event.***

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study. Newborn infants should be followed until 30 days old.

Any pregnancy occurring in a subject or subject's partner from the time of consent to 90 days after the study treatment must be reported and then followed for outcome. If a subject inadvertently becomes pregnant while on study drug treatment, the subject will be immediately discontinued from study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated.

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor **and/or Sponsor's safety designee within 24 hours** of the investigator's knowledge of the event via the study EDC system.

13.0 CORRELATIVE STUDIES AND BIOMARKER EVALUATIONS

13.1 Correlative Studies

Evaluate the effect of NT-I7 when administered after Kymriah on the expansion and function of lymphocytes, CAR T-cells, and serum cytokines in vivo by:

1. Flow cytometry-based comprehensive immunophenotyping of T-cells, T-cell subtypes and myeloid subsets in peripheral blood. Peripheral blood samples will be analyzed by multiparameter flow cytometry developed in the DiPersio lab to quantitate the major classes of T cells (including, but not restricted to, naïve/memory Treg, naïve/central memory/effector memory and other T-cell subsets based on functionality), B lymphocytes, NK cells, monocytes, and dendritic cells. This analysis will capture the major phenotypes described in the NIH Human Immunology Project with additional markers for deeper T cell analyses. The activation state of T cells will be assessed using mAbs including but not limited to CD127, HLA-DR, CD38, CD27, CD28, CD25, KI67, granzyme A, granzyme B, expansion of CART cells and various T cell subtypes will be determined for days 0-21 (prior to NT-I7 administration), days 22-100 (after NT-I7 administration and 3-month post CAR T-cell Therapy infusion).
2. Quantitative DNA PCR and/or FACS for measuring CAR T-cell expansion: Measuring CART levels at various timepoints by flow cytometry and qPCR will be done in collaboration with Navigate BioPharma (a Novartis subsidiary) who have proprietary PCR primers, validated qPCR assays, proprietary anti-Kymriah antibodies and FACS-based assays that will allow us to precisely measure expansion and persistence of CAR T-cell Therapy in response to NT-I7. Peak CART/ μl (C_{max}) and persistence ($T_{1/2}$) before and after NT-I7 will be measured by both FACS and qPCR. Area under the curve (AUC) for CART during days 0-21 (prior to NT-I7 administration), days 22-100 (after NT-I7 administration and 3-month post CAR T-cell Therapy infusion) will be calculated.
3. Serum cytokine profiling: Serum concentrations of relevant cytokines, chemokines and other immune mediators, including but not limited to IL-1 β , IL-2, IL-6, IL-7, IL-10, IL-12p70, INF- α , INF- γ , MCP-1, TNF- α , CXCL9 and CXCL10 will be determined using Luminex® xMAP® technology.
4. Single cell RNA sequencing (scRNA-seq) of peripheral blood before NT-I7 administration, on D35 +/- 2 days (i.e., approximately 2 weeks after NT-I7 administration), and at the time of relapse: Single cell RNA sequencing will be performed as previously described (Sheih, A., et al. Clonal kinetics and single-cell transcriptional profiling of CAR-T cells in patients undergoing CD19 CAR-T immunotherapy. Nat Commun 11, 219 (2020)). Data generated from scRNA-seq

will be used for three main purposes: 1) identify differentially expressed genes (DEGs) in T cells (both CAR T-cells and non-CAR T-cells) that are transcriptionally unique and associated with NT-I7 treatment, 2) perform gene set enrichment analysis (GSEA) to study the effect of NT-I7 on gene sets associated with T cell activation and effector response, and T cell suppression and exhaustion, and 3) determine the effect of NT-I7 on the transcriptional profile of subsets of non-T cells such as B cells and myeloid cells in the peripheral blood.

5. Polyfunctional analyses to assess the number and percentage of CAR T-cell and non-transduced T cells that are able to express and secrete various cytokines and chemokines before NT-I7 administration and on D35 +/- 2 days. Peripheral blood will be subjected to Isoplexis IsoCode Polyfunctional analyses to assess number and percent of CAR T-cell and nontransduced T cells that are able to express and secrete various cytokines and chemokines at the single cell level. For these studies we will use fluorescein-conjugated CD19 extracellular domain to distinguish between CAR T-cells and non-CAR T-cells. Studies will be performed using the Isolite Single Polyfunctional Strength Chip which will allow us to measure both the number of CART19+ and nontransduced cells and the level of 32 different cytokines expressed and secreted by individual -CART19 and nontransduced T cells before and after NT-I7 thus allowing us to generate a "Polyfunctional Strength Index" which has been reported by others to be associated with enhanced CART anti-tumor activity. (Ref1: Fraietta, J.A., et al. Identification of Functional Determinants of Response and Resistance to CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy of Chronic Lymphocytic Leukemia. *Blood* 130, 3181-3181 (2017). Ref2: Bowman, N., et al. Advanced Cell Mapping Visualizations for Single Cell Functional Proteomics Enabling Patient Stratification. *PROTEOMICS* n/a, 1900270. Ref3: Liu, D., Paczkowski, P., Mackay, S., Ng, C. & Zhou, J. Single-Cell Multiplexed Proteomics on the IsoLight Resolves Cellular Functional Heterogeneity to Reveal Clinical Responses of Cancer Patients to Immunotherapies. in *Biomarkers for Immunotherapy of Cancer: Methods and Protocols* (eds. Thurin, M., Cesano, A. & Marincola, F.M.) 413-431 (Springer New York, New York, NY, 2020).
6. LBCL immunophenotyping pre-treatment (before CAR T-cell Therapy infusion), on Day 7, Day 28, and at the time of relapse: This will include but not be limited to IHC and flow for CD19 expression on malignant cells.

To correlate baseline and post-treatment responses as assessed by plasma minimal residual disease (MRD), and compared to SOC FDG PET-CT imaging in the Dose Expansion phase.

13.2 NT-I7 pharmacokinetics (PK) and Immunogenicity (ADA) Analysis

Serum samples will be evaluated for the presence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) to NT-I7, and pharmacokinetic analysis (PK) will be performed to determine concentration of NT-I7. All bioanalytical assays have been validated at BioAgilytix (vendor for PK-ADA studies).

Immunogenicity to NT-I7 will be measured using a risk-based, tiered testing approach. This includes a core assay comprising of screening, confirmatory, and titer testing for detecting anti-drug antibodies (ADA) to NT-I7 as well as an IL-7 epitope-specific assay, and a cell-based neutralizing antibody assay for detecting anti-NT-I7 antibodies that may neutralize IL-7 bioactivity in patient serum samples. Subject samples will be obtained on Day 21 (pre-dose NT-I7), Day 35, Day 49, Day 63, and Day 100 was administered to evaluate the prevalence and incidence of treatment-emergent/boosted ADA.

14.0 DATA MANAGEMENT AND REPORTING

Data collection for this study will be done exclusively through an electronic clinical data management system. The Data Management Organization will utilize a core set of electronic Case Report Forms (eCRF) that are Clinical Data Acquisition Standards Harmonization (CDASH)-complaint (<https://www.cdisc.org/standards/foundational/cdash>). Customized eCRFs will be included when appropriate to meet unique study requirements. The data management organization will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

Access to the study is granted to all persons with the appropriate roles, as listed on the Delegation of Authority Sheet. Upon site activation, all persons with the appropriate roles will be sent a study invitation email. Site users will not be able to access the study until all required study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings).

For further details, please refer to the Site Operations Manual.

14.1 Responsibility for Data Submission

To provide evidence that the protocol has been followed, documentation of all procedures that are conducted under this protocol is required. In cases of screen failures, the following information must be documented within the source: demographic data (including at minimum sex, age and/or birth year, race/ethnicity, and informed consent date), the outcome of the eligibility assessment, the reason for the screening failure by criterion, and AE details.

It is the responsibility of the PI(s) at the site to ensure that all investigators and study staff at the clinical site understand the procedures for data submission per the protocol. Furthermore, the investigator or designee is responsible for submitting protocol-specified data and queries, including safety case processing queries, accurately and in a timely manner to the data management organization via the EDC system; these must be complete and verifiable with the source. The clinical site must appropriately maintain the source for the required period of time – this ensures data integrity and traceability, and protects personal information of study subjects.

The data management organization is responsible for compiling and submitting data of all subjects to the study Sponsor. The EDC data and supporting documents should be available for the Sponsor/designee, auditors, and regulatory authorities to review/retrieve at any time, as required by clinical trial agreements and GCP requirements.

Good Documentation Practices and ALCOA+ principles for data integrity must be followed for all essential documents and other clinical trial-related records. The Sponsor, the delegated CRO, and investigators must organize and securely retain data and other study records for the required time period. These must be available if requested by regulatory authorities, to ensure the reliability of the trial's results.

14.2 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the study Sponsor is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, <https://www.clinicaltrials.gov>. Information posted will allow subjects

to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

14.3 Study Oversight

Responsibility for monitoring the clinical trial lies with the Sponsor or the delegated CRO. The purpose of monitoring is to ensure protection of subjects' human rights, safety, and well-being, to verify that the trial is conducted according to the current protocol and GCP, and that study data reported by the investigator are entered or available in a timely fashion, and are accurate, complete, and verifiable with source documents and other study-related records. Accordingly, the Sponsor or the delegated CRO will assign study monitor(s), who will monitor the study as detailed in planned monitoring procedures. Monitoring is scaled to data generation by sites.

The investigator and the clinical site are required to cooperate with monitoring and auditing by the Sponsor or delegated CRO, as well as inspections by the IRB/IEC and regulatory authorities. As part of this responsibility, during monitoring, auditing, and inspections, all study-related records, including but not limited to source documents, training records, and delegation logs, must be provided upon request by Sponsor monitors/auditors, IRB/IEC, or regulatory authorities. The investigator must also be available to discuss the findings of the monitoring visit or audit. When source documents are directly accessed, the confidentiality of subject identities must be protected in accordance with local and national regulations.

This protocol will adhere to the policies and requirements listed in Site Operations Manual. Protocol waivers (documented prospective approval of requests from an investigator to deviate from the protocol) are prohibited for this study. For specific responsibilities of the PI, and NeoImmuneTech, please refer to the site specific contract and the Form FDA1572.

- Sponsor or Sponsor's designee is responsible for distributing all Investigational New Drug Application (IND) Action Letters or Safety Reports received from the study Sponsor, NeoImmuneTech, to all participating institutions for submission to their individual Institutional Review Boards (IRBs) for action as required.
- Study drugs may be ordered by a participating site only after approved by the study Sponsor, NeoImmuneTech, and officially activated.

14.4 Medical Monitor Coverage

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the principal investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

14.5 Subject Enrollment and EDC

Subject enrollment will be facilitated using the enrollment module in the EDC system. To access the enrollment module, the site user must be assigned the 'Enroll/Randomize subjects' responsibility on the Delegation of Authority Sheet.

Before enrolling a subject in the EDC system, registration staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all subjects have signed an appropriate consent form and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization form (if applicable).

For further instructional information, please refer to the EDC Completion Guidelines.

15.0 STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and methods for the study. If, after the study has begun, but before the conduct of any analysis, changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

15.1 Sample Size and Power Calculation

Dose Escalation phase: 17-42 subjects.

Dose Expansion phase: 15 subjects are planned for enrollment to ensure 13 evaluable subjects. Since the primary goal of the Dose Expansion phase is focused on evaluating toxicity in a larger sample size, the sample size calculation should be based on safety. Any grade CRS has been reported in, approximately, 50% of patients treated with CD19 CAR-T SOC (Kymriah 58%, Yescarta, 92%, Breyanzi 42%) and ~10% of patients will have Grade 3 or higher CRS (Kymriah 22%, Yescarta, 6%, Breyanzi 2%). ICANS are observed in average in 37% of patients treated with CD19 CAR-T SOC (Kymriah 21%, Yescarta, 60%, Breyanzi 30%) and ~14% of patients will have Grade 3 or higher ICANS (Kymriah 12%, Yescarta, 21%, Breyanzi 10%). We calculated our sample size to demonstrate that addition of NT-I7 does not change the safety profile of these therapies. A sample size of 15 patients will allow us to prove that NT-I7-treated patients develop any grade CRS in less than 20% of cases ($n = 3$) and any grade ICANS in less than 13% of cases ($n = 2$).

15.2 Rationale for using ORR at 3 months to explore the preliminary anti-tumor activity (an exploratory endpoint)

Response evaluation with FDG PET-CT or CT at 1 month, 3 months, 6 months and 12 months post CAR T-cell Therapy infusion is standard of care. One-month time point will be very close to NT-I7 injection. 3-month time point is the next best option based on the expected pharmacokinetic and pharmacodynamic effect of NT-I7 and allows assessment of early response post Kymriah and NT-I7 treatment.

15.3 Rationale for ORR threshold

In the JULIET study of Kymriah in adults with r/r DLBCL, the ORR was 50% (34 CRs+PRs out of 68 subjects).

In the ZUMA-1 study of Yescarta in adults with r/r DLBCL, the ORR was 83% (84 CRs+PRs out of 101 subjects). In the ZUMA-7 study these results were replicated with 83% ORR (150 CRs+PRs out of 180 subjects).

In the TRANSCEND study of Breyanzi in adults with r/r DLBCL, the ORR was 73% (186 CRs + PRs out of 256 patients).[\(20\)](#)

15.4 Stratification Factors

The safety population will be stratified based on the type of CD19 CAR T-cell Therapy the subject received. Subjects will be further stratified into two groups based on timing of the EOS visit.

- a. Type of CAR T-Cell Therapy: Kymriah, Yescarta, or Breyanzi
- b. End of Study Visit: < Day 100 or > Day 100

15.5 Interim Analyses

An Interim Analysis will be performed at the completion of the Dose Escalation phase.

15.6 Data and Safety Monitoring Committee (DSMC)

The DSMC is composed of the Protocol PI, Study Medical Monitor, Study Statistician and the Sponsor's CMO or designee. The DSMC will make decision for dose escalation or dose-de-escalation in the Dose Escalation phase. The DSMC will review the data from the Interim Analysis and determine the RP2D. In the Dose Expansion phase, the DSMC will monitor for subject safety and scientific integrity during the study. Details will be described in a separate DSMC Charter.

In addition, the safety of the enrolled subjects will be continuously monitored by the site investigators/staff/Sponsor or Sponsor designee and the Study Stopping Rules ([Section 7.3](#)) will be followed. All immediate safety concerns must be discussed with the Sponsor and/or Sponsor's designee upon occurrence and/or awareness of the event to determine appropriate care for the subject, including whether the subject should continue or discontinue study treatment.

15.7 Statistical Analysis Plan Summary

Endpoints/Statistical Considerations:

- Primary Endpoint for the Phase 1b:
The primary endpoint for the Phase 1b will be the safety and tolerability, including determination of the MTD and/or the RP2D, of NT-I7 when administered after SOC CD19 CAR T-cell Therapy in subjects with r/r LBCL, as assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, except grading for CRS and ICANS will be based on ASTCT guidelines.
 - The MTD will be defined as the dose of NT-I7 that yields a DLT rate $\leq 33\%$. If an MTD is not reached, the highest administered dose evaluated for safety will be 720 $\mu\text{g/kg}$.
 - The DLT period and definition:
 - DLT period: from NT-I7 administration until 21 days after

- DLT definition: Dose-limiting toxicity is defined as any AE occurring within the first 21 days after NT-I7 injection that is considered to be at least possibly, probably, or definitely related to the study treatment (NT-I7) per the investigator, and that meets at least one of the non-hematologic or hematologic criteria listed below.

Hematologic criteria

- Any Grade 5 toxicity
- Grade 4 neutropenia lasting more than 5 days
- Febrile neutropenia of more than 5 days (ANC $<1.0 \times 10^9/L$, fever $\geq 38.5^\circ C$)
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion not recovering to baseline at the end of DLT period
- Grade 4 anemia, unexplained by underlying disease
- Grade 4 hematological toxicities lasting more than 21 days

Non-hematologic criteria

- Any Grade 5 toxicity
- Grade 3 or higher non-hematologic toxicity.
- Hy's law criteria
- Any Grade ≥ 4 CRS or Grade 3 CRS that does not improved to Grade ≤ 1 within 72 hours
- Any Grade ≥ 3 ICANS. Note: Grading of CRS and ICANS is based on ASTCT guidelines

The following exceptions are acceptable (i.e., not considered DLTs).

- Grade 3 or 4 electrolyte abnormalities that lasts < 24 hours to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
 - Grade 3 nausea, vomiting or diarrhea that resolves to Grade 2 or less within 72 hours with symptomatic treatment
 - Grade 3 liver enzyme abnormalities improving to grade 2 or better within 72 hours
- Determination of the RP2D: The RP2D will be based on an accumulation of all available data. All available data including clinical PK, PD, anti-tumor activity (including best ORR) and safety, and nonclinical pharmacology data will be pooled. Integrated dose-response and exposure-response analyses will be conducted to determine the RP2D.

- Sample Size and Justifications:

Dose Escalation phase: 17-42 subjects.

Dose Expansion phase: 15 subjects are planned for enrollment to ensure 13 evaluable subjects.

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17.0 ABBREVIATIONS

Abbreviation	Definition
ABC	activated B cell
ADA	Anti-Drug Antibodies
AE	adverse event
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukemia
AUC	area under the curve
BCMA	B-cell maturation antigen
BIRC	Blinded Independent Review Committee
BLI	bioluminescent imaging
CAR	chimeric antigen receptor
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMR	complete metabolic response
COO	cell of origin
CPA	cyclophosphamide
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
DC	dendritic cell
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DSMC	Data Safety Monitoring Committee
FDG	fluorodeoxyglucose
GCB	germinal center B cell
GZMB	serine protease Granzyme B
GZMK	serine protease Granzyme K
GVHD	graft-versus-host disease
HIV	human immunodeficiency virus
HV	healthy volunteer
hyFc	hybrid Fc region of a human antibody
ICANS	immune effector cell-associated neurotoxicity syndrome
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin

IM	intramuscular
IND	Investigational New Drug
LBCL	large B-cell lymphoma
NAb	Neutralizing antibodies
NHL	non-Hodgkin lymphoma
NIT	NeoImmuneTech, Inc.
NK	natural killer
OR	objective response
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PET	positron emission tomography
PFS	progression-free survival
Ph. Eur	European Pharmacopeia
PMR	partial metabolic response
PR	partial response
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
REMS	Risk Evaluation and Mitigation Strategy
rhIL-7	recombinant human IL-7
rhIL-7-hyFc	NT-I7 (fusion protein comprising human IL-7 fused to the human IgD hinge region, which is fused to the N-terminal region of CH2 from IgD and 2 key regions of the antibody IgG4: C-terminal region of CH2, and the entire CH3 region)
RP2D	recommended Phase 2 dose
r/r	relapsed or refractory
SELL	cell adhesion molecule L-Selectin
SC	subcutaneous
T _{CM}	central memory T cells
T _{EM}	effector memory T cells
T _{EMRA}	terminally differentiated effector memory T cells
T _{max}	time to maximum plasma concentration
T _N	naïve T cells
TNF	tumor necrosis factor
T-reg	regulatory T cells
T _{SCM}	memory stem cell
UCART19	Anti-CD19 universal CAR-T
WBC	white blood cell