Protocol 18-255-01

A PHASE 2/3, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF NKTR-255 VS PLACEBO FOLLOWING CD19-DIRECTED CAR-T CELL THERAPY IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA

NCT05664217

Approval Date: 08 October 2022

Nektar Therapeutics

CLINICAL STUDY PROTOCOL

A PHASE 2/3, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF NKTR-255 VS PLACEBO FOLLOWING CD19-DIRECTED CAR-T CELL THERAPY IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA

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Eudra CT Number:	CCI [redacted]
Investigational Product:	NKTR-255
Indication:	Non-Hodgkin Lymphoma (large B-cell lymphoma)
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA PPD [redacted]
Sponsor's Medical Contact and Study Medical Monitor:	PPD [redacted] PPD [redacted] Nektar Therapeutics PPD [redacted]

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INVESTIGATOR SIGNATURE PAGE

Nektar Therapeutics

TITLE:	**A PHASE 2/3, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF NKTR-255 VS PLACEBO FOLLOWING CD19-DIRECTED CAR-T CELL THERAPY IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	18-255-01
PHASE OF STUDY:	2/3
PROTOCOL DATE:	08 October 2022
STUDY SPONSOR:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

PRINCIPAL INVESTIGATOR COMMITMENT:

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that I understand my responsibilities pursuant to the Code of Federal Regulations (21 CFR § 312) and ICH E6 Good Clinical Practice guidelines, as well as with any and all applicable federal, state and/or local laws and regulations, and agree to conduct the study in accordance with the protocol referenced herein.

_____

Principal Investigator Printed Name

_____ _____

Principal Investigator Signature **Date**

Institution:

Address:

PROTOCOL APPROVAL PAGE

A PHASE 2/3, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF NKTR-255 VS PLACEBO FOLLOWING CD19-DIRECTED CAR-T CELL THERAPY IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA

PROTOCOL NUMBER: 18-255-01

PHASE: 2/3

PROTOCOL DATE: 08 October 2022

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Serious AE and Pregnancy Reporting	PPD	

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CCI [redacted]

CCI [redacted]

CCI [redacted]



ABBREVIATIONS

Abbreviation or Term	Definition
ACG	absolute granulocyte count
ACS	American Cancer Society
CCI	[redacted]
AE	adverse event
AESI	adverse event of special interest
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ALP	alkaline phosphatase
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
ASTCT	American Society for Transplant and Cellular Therapy
AUC	area under the curve
$AUC_{0\text{-}28d}$	area under the curve from Days 0 to 28
AUC_{last}	area under the curve from time 0 to last measurable concentration
axi-cel	axicabtagene ciloleucel
B-ALL	B-cell acute lymphoblastic leukemia
BICR	blinded independent central review
BOR	best overall response
BUN	blood urea nitrogen
C1D1, C1D15	cycle 1 day 1, cycle 1 day 15
CAR-T	chimeric antigen receptor T (cell)
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatinine kinase
CL	clearance
C_{max}	maximum concentration
CMH	Cochran-Mantel Haenszel
CNS	central nervous system
CR	complete response
CRR3, CRR6	complete response rate at month 3, complete response rate at month 6
CRC	colorectal carcinoma
CRF	case report form

Abbreviation or Term	Definition
CRP	C reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CCI	[redacted]
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLCO	diffusing capacity of the lung for carbon monoxide
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
DSMC	Data and Safety Monitoring Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
EOT	end of treatment
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FDG	18F-fluorodeoxyglucose
FIH	first-in-human
FISH	Fluorescence in situ hybridization
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
GVHD	graft versus host disease
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin

Abbreviation or Term	Definition
HCT	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
ICANS	immune effector cell associated neurotoxicity
ICE	immune effector cell-associated encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation
ICP	intracranial pressure
IEC	Independent Ethics Committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IL-15R, IL-15Rα	interleukin-15 receptor, interleukin-15 receptor alpha subunit
CCI [redacted]	[redacted]
IND	Investigational New Drug application
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	Interactive Response Technology
ISC	Independent Statistical Center
ITT-S1 CCI [redacted]	Intent-to-Treat Population Stage 1, CCI [redacted]
IV	intravenous
IVIG	intravenous immunoglobulin
JAK	Janus kinase
kDa	kilodalton
LBCL	large B-cell lymphoma
LD/LDC	lymphodepletion chemotherapy
LDH	lactate dehydrogenase

Abbreviation or Term	Definition
liso-cel	lisocabtagene maraleucel
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCP-1	monocyte chemoattractant protein-1
MCV	mean corpuscular volume
mg	milligram
min	minute(s)
mL	milliliter
MM	multiple myeloma
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple uptake gated acquisition
CCI	[redacted]
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin lymphoma
NK	natural killer
NKT	natural killer T (cells)
NYHA	New York Heart Association
ORR	objective response rate
ORR3, ORR6	objective response rate at month 3, objective response rate at month 6
OS	overall survival
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
CCI	[redacted]
PEG	polyethylene glycol
PET	positron emission tomography

Abbreviation or Term	Definition
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetic
CCI [redacted]	[redacted]
PO	orally
PR	partial response
PR–	progesterone-receptor-negative
PT	prothrombin time
PTT	partial thromboplastin time
q21d, q28d	every 21 days, every 28 days
q3w, q4w	every 3 weeks, every 4 weeks
qPCR	quantitative polymerase chain reaction
QTcF	Fridericia's corrected QT interval
RBC	red blood cells
RE-S1	Response-Evaluable Population-Stage 1
rh	recombinant human
RP2D	recommended Phase 2 dose
RP3D	recommended Phase 3 dose
R/R	relapsed or refractory
SAE	serious adverse event
SaO_2	oxygen saturation on room air
SAP	statistical analysis plan
SD	stable disease
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
Safety-S1, CCI [redacted]	Safety Population for Stage 1, CCI [redacted]
STAT5	signal transducer and activator of transcription 5
sTNFRI, sTNFRII	soluble tumor necrosis factor receptor I, soluble tumor necrosis factor receptor II
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
T3	triiodothyronine
T4	free thyroxine

Abbreviation or Term	Definition
TEAE	treatment-emergent adverse event
CCI	[redacted]
T_{last}	Time to last measurable concentration
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TP	total protein
TSH	thyroid stimulating hormone
ULN	upper limit of normal
Vd	volume of distribution
WBC	white blood cell

1.0 STUDY SYNOPSIS

<table>
<tr><td>Title of Study:</td><td>A Phase 2/3, randomized, double blind, placebo-controlled, multicenter study of NKTR-255 vs placebo following CD19-directed CAR-T cell therapy in patients with relapsed/refractory large B-cell lymphoma</td></tr>
<tr><td>Sponsor:</td><td>Nektar Therapeutics</td></tr>
<tr><td>Name of Finished Product(s):</td><td>NKTR-255 drug product</td></tr>
<tr><td>Name of Active Ingredient(s):</td><td>NKTR-255 drug substance</td></tr>
<tr><td>Standard of Care Treatment Prior to NKTR-255:</td><td>CD19-directed chimeric antigen receptor T (CAR-T) cell therapy: axicabtagene ciloleucel or lisocabtagene maraleucel (Stages 1 CCI), CCI CCI</td></tr>
<tr><td>Phase of Development:</td><td>Phase 2/3</td></tr>
<tr><td>Objectives:</td><td>
<table>
<tr><th></th><th>Stage 1</th></tr>
<tr><td>Primary Objective(s)</td><td>To compare the CR rate by BICR at month 6 of treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.</td></tr>
<tr><td>Secondary Objectives</td><td>• To evaluate the safety and tolerability of NKTR-255 vs placebo in patients following treatment with CD19-directed CAR-T cell therapy.
• To compare the CR rate by BICR at month 3, the ORR by BICR at month 3 and 6, best CR rate and ORR following treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.
• To compare DOR, and PFS by BICR, EFS[a], and OS following treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.</td></tr>
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	 BICR = blinded independent central review; CAR-T cell = chimeric antigen receptor T cell; CR = complete response; CCI DOR = duration of response; EFS = event-free survival; CCI CCI ORR = objective response rate; OS = overall survival; CCI ; PFS = progression-free survival; CCI a. Event-free survival is defined as the time from randomization to the earliest date of disease progression by BICR per Lugano Classification, commencement of new lymphoma therapy, or death from any cause.
Duration of Treatment:	Study drug (NKTR-255 or placebo) infusion will be started no earlier than Day 14 (+7 days) after CAR-T cell infusion and administered every 3 weeks (q3w) for up to 7 cycles or 5 months, whichever is earlier. The last dose of study drug is to be given at least 28 days before the positron emission tomography (PET)/computed tomography (CT) scan conducted at 6 months post CAR-T cell infusion. Study drug may be stopped if there is unacceptable toxicity, the patient withdraws treatment consent, the Investigator/designee determines it is not in the patient's best interest to continue with study drug infusions, disease progression, or the study is terminated by the Sponsor.
Study Population:	Adults aged 18 years and older with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) receiving CD19-directed CAR-T cell therapy.

CCI

Study Design:	This is a Phase 2/3, multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of NKTR-255 versus placebo following CD19-directed CAR-T cell therapy in patients with R/R LBCL. The study is conducted CCI , with routine safety monitoring being conducted by the Data Monitoring Committee (DMC) on a regular basis: • In **Stage 1** (Phase 2), patients with R/R LBCL being treated with commercial CAR-T cell therapy will be randomized (following CAR-T cell therapy) in a CCI to receive either 1.5 µg/kg NKTR-255, 3.0 µg/kg NKTR-255, a step-up dose regimen initiating with 3.0 µg/kg NKTR-255 in Cycle 1 (C1) and continuing in Cycle 2 and subsequent cycles (C2+) with 6.0 µg/kg NKTR-255 (hereinafter referred to as 3.0/6.0 µg/kg NKTR-255), or placebo CCI . Randomization will be stratified by: • Cellular product (ie, axicabtagene ciloleucel [axi-cel] or lisocabtagene maraleucel [liso-cel]) • Baseline lactate dehydrogenase (LDH) (≥ 440 U/L or < 440 U/L prior to lymphodepletion confirmed by central laboratory) Once patients meet criteria for study drug administration, patients will be treated with study drug (ie, NKTR-255 at 1.5, 3.0, 3.0/6.0 µg/kg, or placebo) given by intravenous (IV) infusion. Patients must be premedicated with an antihistamine (H1 receptor blocker such as diphenhydramine [25 mg orally or IV equivalent]) and acetaminophen (500 to 650 mg orally or equivalent) between 30 and 60 minutes before each infusion of study drug. Study drug will be administered q3w for up to 7 cycles or 5 months, whichever is earlier, starting on Cycle 1 Day 1 (C1D1). Each cycle will be 21 days. Patients must meet prespecified dosing criteria prior to each infusion of study drug: • For Cycle 1, dosing should occur 14 days after CAR-T cell therapy but may be delayed up to 7 days until a patient meets the randomization criteria (ie, maximum period between CAR-T cell therapy and study drug infusion on C1D1 is 21 days). • For Cycle 2 and beyond, dosing may be delayed up to a maximum of 21 days until a patient meets dosing criteria. The DMC will review all available safety, CCI data after approximately CCI patients CCI have completed 2 cycles of study drug treatment. Following DMC review of data from the initial CCI patients, the dose of NKTR-255 may be escalated for any cohort(s) for the remainder of patients randomized in Stage 1. Dose escalation will not exceed double the prior dose of NKTR-255. Additionally, cohort dose optimization (including C1) or closure of any cohorts may occur based on safety, CCI data review. An enrollment pause will be implemented at the end of Stage 1 CCI , and the DMC will review safety and efficacy data from all available cohorts to make go/no-go and dose selection recommendations CCI . The study team will be unblinded at

	the end of Stage 1 to review totality of the data including efficacy, safety, CCI data before the study proceeds CCI . CCI
CCI	
Key Eligibility Criteria:	**Inclusion Criteria (Stages 1 CCI):** Within the Screening Period and, unless noted otherwise, prior to leukapheresis, patients must meet all the following criteria to be randomized in this study. Informed consent must be signed prior to any study-specific procedures. 1) Male or female ≥ 18 years of age at the time of consent. 2) Received standard of care therapy with axi-cel or liso-cel CCI , for the following respective Food and Drug Administration (FDA) (or Summary of Product Characteristics [SmPC]) approved indication(s): a) liso-cel: Patients with LBCL (including diffuse LBCL [DLBCL] not otherwise specified [including DLBCL arising from indolent lymphoma], high-grade B-cell lymphoma, primary mediastinal LBCL, and follicular lymphoma Grade 3B), who have: (1) refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; (2) 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, (3) relapsed or refractory disease after two or more lines of systemic therapy. b) axi-cel: For the treatment of adult patients with LBCL that is: (1) refractory to first-line chemoimmunotherapy; (2) relapses within 12 months of first-line chemoimmunotherapy; or, (3) R/R LBCL after 2 lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal LBLC, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. CCI

	3) Received lymphodepleting chemotherapy regimen according to the respective FDA (or SmPC) label for CAR-T cell therapy. 4) Fluorodeoxyglucose (FDG)-avid disease on PET imaging within 30 days prior to CAR-T cell infusion. 5) FDG avid lesion(s) on PET/CT scan following bridging therapy and prior to lymphodepletion, where applicable. 6) Evidence of CD19 expression on any prior or current NHL tumor specimen or a high likelihood of CD19 expression based on disease histology per investigator's assessment. 7) Within 7 days before leukapheresis, patient should have an Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1. 8) Regarding prior systemic anti-tumor therapy: a) At least 3 months have elapsed since systemic immune checkpoint inhibitory/immune stimulatory therapy (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc). b) At least 2 weeks have elapsed since other prior systemic antitumor therapy. c) Bridging therapy (including steroids) is permitted between leukaphoresis and lymphodepletion as long as Exclusion Criterion 1 is satisfied. 9) Adequate organ function, defined as: a) Adequate bone marrow function (prior to lymphodepletion) for lymphodepletion chemotherapy defined as: absolute neutrophil count (ANC) $\geq$ 1000 cells/mm^3, platelets $\geq$ 50,000 cells/mm^3, and hemoglobin $\geq$ 8 g/dL in the absence of bone marrow involvement by lymphoma. No transfusion within 3 days of bone marrow function assessment; growth factor support is allowed as per institutional practice. b) Calculated creatinine clearance (Cockcroft/Gault) > 30 mL/min. c) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$ 3 × upper limit of normal (ULN; or < 5 × ULN for patients with lymphomatous infiltration of the liver) and total bilirubin $\leq$ 2 × ULN (or < 3.0 × ULN for patients with Gilbert's syndrome or lymphomatous infiltration of the liver). d) Adequate pulmonary function, oxygen saturation on room air (SaO_2) $\geq$ 92%. Patients with a history of interstitial lung disease should undergo pulmonary function testing and must have a forced expiratory volume in 1 second (FEV_1) of $\geq$ 50% of predicted value or diffusing capacity of the lung for carbon monoxide (DLCO; corrected) $\geq$ 40% of predicted value. e) Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) $\geq$ 40% as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition (MUGA) within 60 days before randomization. 10) Electrocardiogram (ECG) demonstrating Fridericia's corrected QT interval (QTcF) < 470 ms. Patients with QTcF $\geq$ 470 ms will require clearance by a local cardiologist. 11) Women of reproductive potential (defined as all women physiologically capable of becoming pregnant) must agree to use suitable methods of contraception from the start of study treatment until 1 month after the last dose of study drug. 12) Males who have partners of reproductive potential must agree to use an effective barrier contraceptive method from the start of study treatment until 1 month after the last dose of study drug.

	13) Ability to understand and provide written informed consent. 14) Able and willing to comply with study visit schedule and procedures, including tumor biopsy where accessible. **Additional Eligibility Criteria Following CD19-Directed CAR-T Cell Infusion (Stages 1 and 2):** Patients who have received commercially released CAR-T cell infusion must satisfy the following criteria on the day of randomization: 15) No fever ≥ 38.0°C/Grade ≥ 1 cytokine release syndrome (CRS; American Society for Transplant and Cellular Therapy [ASTCT] criteria [Lee 2019]) within 24 hours. 16) No Grade ≥ 3 CRS (ASTCT criteria) within 72 hours. 17) No previous Grade ≥ 3 immune effector cell-associated neurotoxicity syndrome (ICANS) of > 72 hours duration. 18) No Grade ≥ 2 ICANS (ASTCT criteria). 19) No tocilizumab and/or dexamethasone within 48 hours. 20) No active, serious, and/or uncontrolled infection(s) 21) No other contraindication according to the Investigator's assessment. 22) Patients must satisfy the following local laboratory test results: • ANC or absolute granulocyte count (AGC) ≥ 1000/µL • Platelets ≥ 30,000/µL • Hemoglobin ≥ 8 g/dL • Leukocytes ≥ 3000/µL Randomization should occur no more than 1 day before the first study drug infusion. **Exclusion Criteria (Stages 1 and 2):** 1) Use of therapeutic doses of corticosteroids (≥ 5mg/day prednisone or equivalent) or other systemic immunosuppression within 7 days prior to leukapheresis or within 72 hours prior to CAR-T cell infusion. Topical and/or inhaled steroids are permitted. 2) Prior treatment with any CD19-directed CAR-T cell therapy other than the treatment planned per Inclusion Criterion 2. 3) For allogeneic hematopoietic cell transplant recipients, active graft versus host disease (GVHD) and/or systemic GVHD therapy during screening or up to 30 days prior to leukapheresis. 4) Known active hepatitis B (detectable hepatitis B DNA) or hepatitis C (detectable hepatitis C RNA). 5) Known human immunodeficiency virus (HIV) infection. 6) Pregnant or breastfeeding women. 7) Prior treatment with any interleukin (IL)-2 or IL-15 agonist and/or biosimilar agents. 8) Active autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, ulcerative colitis, Crohn's disease], celiac disease, or other serious chronic gastrointestinal conditions associated with diarrhea, autoimmune vasculitis, systemic lupus erythematosus, Wegener syndrome [granulomatosis with polyangiitis], myasthenia gravis, Graves' disease,

	rheumatoid arthritis, hypophysitis, uveitis, etc.) within 1 year prior to randomization. The following are exceptions to this criterion: a) Vitiligo b) Alopecia c) Hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement d) Type 1 diabetes mellitus e) Psoriasis not requiring systemic treatment f) Conditions considered to be low risk of serious deterioration by the Investigator and with Medical Monitor approval
	9) History of any one of the following cardiovascular conditions within the 6 months prior to randomization: class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, or unstable angina; unless clearance by a cardiologist is obtained. 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.
	10) History or presence of clinically relevant central nervous system (CNS) pathology, such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, or psychosis that in the opinion of the Investigator is a contraindication to study treatment.
	11) History of CNS lymphoma, primary CNS lymphoma, brain metastases, or detectable malignant cells in the cerebrospinal fluid.
	12) History of solid organ transplantation.
	13) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Medical Monitor.
	14) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted.
	15) Active or current participation on any other interventional studies.
	16) Use of an investigational agent or an investigational device within 28 days of CAR-T cell therapy
	17) Live, attenuated vaccines are prohibited within 30 days of randomization.
	18) Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of results.

Criteria for Dosing:	1) No fever ≥ 38.0°C/Grade ≥ 1 CRS (ASTCT criteria) within 24 hours of the planned study drug infusion. 2) No Grade ≥ 3 CRS (ASTCT criteria) within 72 hours preceding the study drug infusion. 3) No Grade ≥ 2 ICANS (ASTCT criteria) on the day of the study drug infusion. 4) No previous Grade 4 infusion-related reaction to study drug infusion (Cycle 2 and beyond). 5) No tocilizumab and/or dexamethasone within 48 hours preceding the study drug infusion. 6) No active, serious, and/or uncontrolled infection(s) on the day of the planned study drug infusion. 7) Patients must have the following laboratory test results (ie, within 24 hours): • ANC or AGC ≥ 1000/μL • Platelets ≥ 30,000/μL • Hemoglobin ≥ 8 g/dL • Leukocytes ≥ 3000/μL
Test Product, Dose and Mode of Administration:	NKTR-255 will be administered by IV infusion q3w starting no earlier than Day 14 following CD19-directed CAR-T cell infusion. NKTR-255 will be infused over 30 ± 5 minutes. In Stage 1, NKTR-255 will be dosed at 1.5 μg/kg, 3.0 μg/kg and 3.0/6.0 μg/kg. CCI [redacted]
Comparator Product, Dose and Mode of Administration:	Placebo is commercially available 0.9% Sodium Chloride Solution for Injection (USP). Placebo will be administered by IV infusion q3w starting no earlier than Day 14 following CD19-directed CAR-T cell infusion. Placebo will be identical to NKTR-255 in appearance and will be infused over 30 ± 5 minutes.
Safety:	Assessment of safety will occur by ongoing review of the following: • Incidence of adverse events (AEs), including serious AEs (SAEs) • Clinical laboratory tests (blood and urine sampling) • Vital signs • ECG • Physical examination • ECHO/MUGA Adverse events of special interest (AESI) include CRS and ICANS and will be graded according to ASTCT criteria (Lee 2019). Other AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 (CTCAE 2017).

[redacted]
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[redacted]

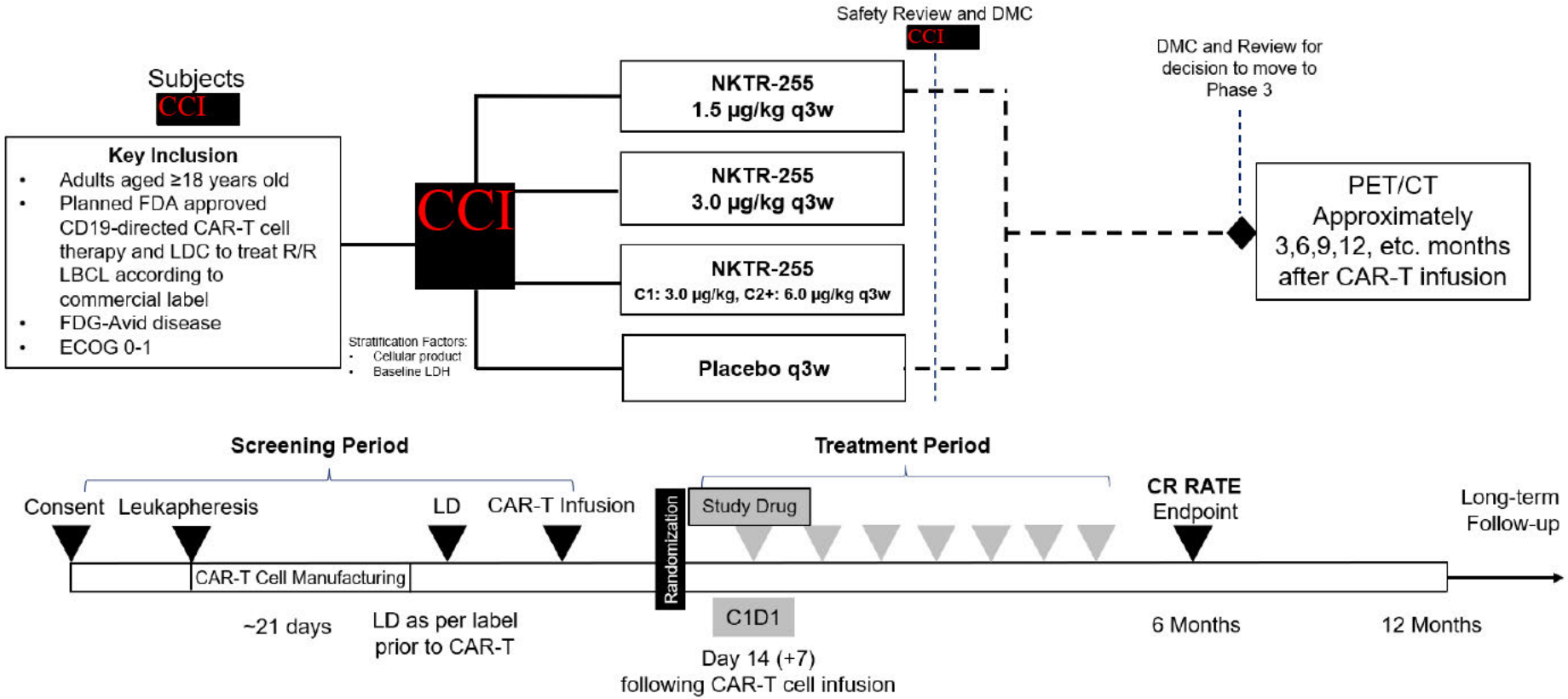
Efficacy:	PET/CT will be performed at baseline and for assessment of response at approximately 3, 6, 9, 12, 18, 24 and 36 months following CD19-directed CAR-T cell infusion. Lugano criteria will be used to evaluate the protocol-specified efficacy endpoints. Bone marrow aspirate/biopsy should be performed to confirm complete response (CR) for patients who have radiographic CR and had known or indeterminant bone marrow involvement at baseline. Images will be submitted to a central imaging vendor for BICR.

Statistical Methods:	**Safety:** Safety analyses will be performed CCI [redacted]. For each stage, safety assessments will include AEs, clinical laboratory tests, vital signs, physical examinations, ECGs, and cardiac function. All Grade ≥ 3 treatment-emergent AEs (TEAEs) will be summarized by system organ class and preferred term. TEAEs will be summarized by incidence, cycle, severity, and relationship to study drug(s). A table presenting number and percentage of patients with post-baseline severity grade increased from baseline (any Grade, Grade 3-4) by treatment group will be provided.
	Efficacy: Efficacy analyses will be performed CCI [redacted]. There is one planned interim analysis within CCI [redacted] the study. For Stage 1, CR rate at month 6 (CRR6), CR rate at month 3 (CRR3), ORR at month 3 (ORR3), ORR at month 6 (ORR6), best CR and OR rates, DOR, EFS, PFS and OS will be assessed in the Intent-to-Treat Population (ITT-S1) and Response-Evaluable Population (RE-S1), where DOR will be analyzed among responders. The number based on the exact method. The Kaplan-Meier method will be used to summarize the median and 95% CI, along with the 25% and 75% quartiles for EFS, PFS, OS, and DOR.and percentage of patients with CR and OR at month 6, best ORR, and best CRR will be calculated by treatment groups along with the 95% confidence intervals (CIs) CCI [redacted] The interim analysis will be the only and final analysis for CR rate at month 6. CRR6 will be compared using a Cochran-Mantel Haenszel (CMH) test stratified by the stratification factors at a 0.01 (two-sided) alpha level. The CRR6 difference between the two treatment arms with its 95% and 99% CI will be provided. Construction of CIs for the common risk difference will be based on the Mantel-Haenszel estimate adjusting for stratification factors. Breslow-Day test will be performed to test the homogeneity between strata. The CRR6 and its corresponding 95% exact CI will also be calculated by Clopper-Pearson method for each arm. For EFS, the exact timing of the interim analysis within the range of 140 and 224 EFS events will be determined by the observed CRR6 from Stage 1; the final analysis will occur at 280 EFS events. The overall Type I error rate is 0.04 (2-sided) for EFS. The alpha spending at the interim analysis and the final analysis will depend on the exact timing of the interim analysis. The comparison of EFS between the selected NKTR-255 dose vs. placebo will be made based on the stratified log-rank test. A stratified Cox proportional hazards model will be used to estimate the hazard ratio and corresponding 95% CI. The Kaplan-Meier method will also be used to summarize the median and its 95% CI, along with the 25% and 75% quartiles by arm. Other binary endpoints will be analyzed similarly as for CRR6. PFS and OS will be analyzed similarly as for EFS. For DOR, the Kaplan-Meier method will be used to summarize the median and its 95% CI, along with the 25% and 75% quartiles by arm.

	The responses based on the BICR assessment will be the primary analysis method. The responses based on Investigator's assessment may also be assessed as sensitivity analyses.
[redacted]	

1.1 Study Schematics

Figure 1: Stage 1 Study Schema: NKTR-255/Placebo and CD19-Directed CAR-T Cell Therapy



~ = approximately; C1 = Cycle 1; C2+ = Cycle 2 and beyond; C1D1 = Cycle 1 Day 1; CAR-T cell = chimeric antigen receptor T cell (axi-cel or liso-cel); CR = complete response; CT = computed tomography; DMC = Data Monitoring Committee; ECOG = Eastern Cooperative Oncology Group; FDG = ^{18}F-fluorodeoxyglucose; LBCL = large B-cell lymphoma; LD/LDC = lymphodepletion chemotherapy; LDH = lactate dehydrogenase; PET = positron emission tomography; q3w = every 3 weeks; R/R = relapsed or refractory

Notes:

- Patient may sign consent any time prior to lymphodepletion
- CD19-directed CAR-T cell therapy includes axi-cel or liso-cel.
- Randomization will be stratified according to the cellular product that the patient receives (ie, axi-cel or liso-cel) and baseline LDH, and should take place no more than 1 day prior to the first study drug administration.


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1.2 Schedule of Events

Table 1: Stage 1: Schedule of Visits and Assessments

	Screening Period					Randomization[x]	Treatment Period (21-day Cycles)[a]													Post-treatment Period		
	Pre-LD	LD	CAR-T Cell Infusion	Post CAR-T Cell Infusion Day			Cycle 1						Cycle 2					Cycle 3+		EOT[b] 7 (± 3) days	Safety Follow-up 30 (+3) days[c]	Long-term Follow-up[aa]
				1	7																	
Day	~40 days prior to randomization						1[o]	2	4 (±1)	6 (±1)	10 (± 1)	15 (± 1)	1 (± 2)	2	4 (±1)	6 (±1)	10 (± 1)	1 (± 2)	10 (± 2)			
Inclusion/exclusion criteria	X					X																
Confirmation of diagnosis	X																					
Informed consent/ HIPAA	X																					
Medical history[d]	X																					
Physical exam[e]	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ICE score			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height/weight[e]	X						X						X					X		X		
ECOG	X						X						X					X				
Pregnancy test[f] (WCBP)	X[f]						X						X					X		X	X	
Vitals signs including pulse oximetry	X		X	X	X	X	X[g]	X	X	X	X	X	X[g]	X	X	X	X	X	X	X	X	
Chest x-ray	X																					
12-lead ECG	X						X[h]						X[h]					X		X		
MUGA/ECHO	X																			X		
Bone marrow aspirate/biopsy	X[i]											X[p]								As clinically indicated[p]		

Table 1: Stage 1: Schedule of Visits and Assessments (Contd)

	Screening Period					Randomization[x]	Treatment Period (21-day Cycles)[a]													Post-treatment Period		
				Post CAR-T Cell Infusion Day			Cycle 1						Cycle 2					Cycle 3+				
	Pre-LD	LD	CAR-T Cell Infusion	1	7															EOT[b] 7 (± 3) days	Safety Follow-up 30 (+3) days[c]	Long-term Follow-up[aa]
Day	**~40 days prior to randomization**						1[o]	2	4 (±1)	6 (±1)	10 (± 1)	15 (± 1)	1 (± 2)	2	4 (±1)	6 (±1)	10 (± 1)	1 (± 2)	10 (±2)			
Lumbar puncture/ CSF evaluation[j]	X						As clinically indicated															
PET/CT[k]	X						At 3 months (± 10 days) , then 6, 9, 12, 18, 24 and 36 months (± 14 days) after CAR-T cell therapy[q]																
Leukapheresis[u]	X																					
Lympho-depleting chemotherapy		X																				
CAR-T cell infusion			X																			
Randomization[x]						X																
Confirm dosing criteria met prior to NKTR-255 or placebo administration						X	X						X					X				
Premedication[z]							X						X					X				
NKTR-255 or placebo administration							X						X					X				
Safety Evaluations																						
Neurological exam	X			X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]	
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Stage 1: Schedule of Visits and Assessments (Contd)

	Screening Period					Randomization[x]	Treatment Period (21-day Cycles)[a]													Post-treatment Period		
	Pre-LD	LD	CAR-T Cell Infusion	Post CAR-T Cell Infusion Day			Cycle 1						Cycle 2					Cycle 3+		EOT[b] 7 (± 3) days	Safety Follow-up 30 (+3) days[c]	Long-term Follow-up[aa]
				1	7																	
Day	**~40 days prior to randomization**						**1[o]**	**2**	**4 (±1)**	**6 (±1)**	**10 (± 1)**	**15 (± 1)**	**1 (± 2)**	**2**	**4 (±1)**	**6 (±1)**	**10 (± 1)**	**1 (± 2)**	**10 (± 2)**			
Laboratory Evaluations[w]																						
CBC, differential, platelet count	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X
Basic metabolic panel/ additional labs (Appendix 2)	X	X	X	X	X		X				X		X				X	X	X	X	X	X
Urinalysis	X	X	X	X	X		X				X		X				X	X	X	X	X	
Hepatic function panel with LDH	X	X	X	X	X		X				X		X				X	X	X	X	X	X
Uric acid	X	X	X	X	X		X				X		X				X	X	X	X	X	
Serum CRP	X		X	X	X		X				X		X				X	X	X	X	X	
Serum ferritin	X		X	X	X		X				X		X				X	X	X	X	X	
Serum IL-6			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PT, PTT, fibrinogen, and D-dimer	X		X	X	X		X				X		X				X	X	X	X	X	
Quantitative serum IgG	X												X					X		X[m]	X[m]	X[m]
Virology panel (Section 5.8.13)	X																					


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Table 1: Stage 1: Schedule of Visits and Assessments (Contd)

	Screening Period					Randomization[x]	Treatment Period (21-day Cycles)[a]												Post-treatment Period		
	Pre-LD	LD	CAR-T Cell Infusion	Post CAR-T Cell Infusion Day 1	Post CAR-T Cell Infusion Day 7		Cycle 1						Cycle 2					Cycle 3+		EOT[b] 7 (± 3) days	Safety Follow-up 30 (+3) days[c]	Long-term Follow-up[aa]
Day	~40 days prior to randomization						1[o]	2	4 (±1)	6 (±1)	10 (± 1)	15 (± 1)	1 (± 2)	2	4 (±1)	6 (±1)	10 (± 1)	1 (± 2)	10 (± 2)			
Subsequent anticancer therapies/survival/ secondary malignancy information[v]																						X

~ = approximately; AE = adverse events; C1D1 = Cycle 1 Day 1; CAR-T cell= chimeric antigen receptor T cell CCI ; CBC = complete blood count; CNS = central nervous system; CR = complete response; CRP = C-reactive protein; CSF = cerebrospinal fluid; CT = computed tomography; CCI CCI ECG =electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; FCM = flow cytometry; HIPAA = Health Insurance Portability and Accountability Act of 1996; ICE = immune effector cell-associated encephalopathy; IgG = immunoglobulin G; IL-6 = interleukin-6; IVIG = intravenous immunoglobulin; LD = lymphodepletion; LDH = lactate dehydrogenase; MUGA = multiple uptake gated acquisition; PBMC = peripheral blood mononuclear cell; CCI ; PET = positron emission tomography; PT = prothrombin time; PTT = partial thromboplastin time; qPCR = quantitative polymerase chain reaction; SAE = serious adverse event; WCBP = women of childbearing potential

Note: Scheduled timepoint visits cannot be combined, unless specified (eg, EOT and Safety follow-up).

a. Patients will be treated from C1D1 for up to 7 cycles of NKTR-255 or placebo, or 5 months, whichever is earlier. The last dose of study drug is to be given at least 28 days before the PET/CT scan conducted at 6 months post CAR-T cell infusion.

b. End of Treatment (EOT) is to be performed 7 days (± 3 days) after study treatment is discontinued, or before a new antineoplastic regimen has been initiated. If the decision to discontinue study drug is > 20 days after last dose, EOT can be combined with the Safety Follow-up visit.

c. Safety follow-up visit to occur 30 days (+ 3 days) after the last dose of study treatment. After 30 days, only SAEs should be collected during long-term follow-up according to Section 7.7. CCI

d. Medical history prior to first dose of study drug to include hematologic, flow cytometric, histologic, and genetic findings at diagnosis and as well as prior therapies and response to therapy.

e. A full physical examination is required pre-lymphodepletion, at 7 days post CAR-T cell infusion, on Day 1 of each cycle, and EOT; symptom-directed physical examinations can be conducted at all other times. Weight required at screening/baseline, Day 1 of each cycle, and EOT; height required only at screening.

f. Pregnancy tests to be conducted prior to initiation of lymphodepleting chemotherapy and study drug infusion. Pregnancy test during screening needs to be serum; all subsequent visits will be urine pregnancy tests.

g. For C1D1 and C2D1, vital signs, including oxygen saturation, are obtained 30 minutes before the start of infusion; at the completion of each bag or syringe; and 30 min (± 10 min), 60 min (± 10 min), and 2 hours (± 10 min) after the end of infusion.

h. 12-lead ECG to be obtained prior to study drug infusion and at the end of infusion on C1D1 and C2D1. Patients must be resting quietly in the supine position for ≥ 5 minutes prior to collection of 12 lead ECG. CCI [redacted]

i. Bone marrow aspirate/biopsy required for any patient with a history of bone marrow involvement by lymphoma or unexplained cytopenias, unless a negative bone marrow evaluation was performed within 30 days prior to scheduled CAR-T cell infusion. Bone marrow aspirate/biopsy may be omitted in patients who have had a marrow aspirate and biopsy within 30 days before the scheduled CAR-T cell infusion AND have not received antitumor therapy in the interim.

j. Lumbar puncture/CSF evaluation required for any patient with a history of CNS disease or signs and symptoms of CNS or epidural disease unless a negative lumbar puncture was performed within 30 days of scheduled lymphodepleting chemotherapy and as clinically indicated.

k. PET/CT scans (preferably diagnostic quality) to include neck, chest, abdomen and pelvis, as clinically indicated. If a PET/CT is not performed, the CT scan must be of diagnostic quality (contrast-enhanced). Restaging evaluations are not required if the patient proceeds to other antitumor therapy. If dosing and scan days coincide on the same day, scan(s) should occur prior to infusion. Patients who receive cytoreductive bridging therapy must have a PET/CT after completion of bridging therapy and prior to CAR-T cell infusion. Imaging studies may be omitted in patients who have had recent imaging within 30 days before the scheduled CAR-T cell infusion AND have not received anti-tumor therapy in the interim. Bone marrow aspirate/biopsy should be performed to confirm CR for patients who have radiographic CR and had known or indeterminant bone marrow involvement at baseline.

l. A neurologic examination should be performed if there is clinical suspicion of neurologic dysfunction (see Section 5.8.7).

m. Quantitative IgG to be measured during long-term follow-up visits at 9, and 12, 18, 24 and 36 (± 14 days) months after CAR-T cell infusion until levels are normal without IVIG replacement.

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o. C1D1 to occur 14 days (+ 7 days) post CAR-T cell infusion.

p. To be completed 1 month (± 7 days) after CAR-T cell infusion. Also, bone marrow aspirate/biopsy should be performed to confirm CR for patients who have radiographic CR and had known or indeterminant bone marrow involvement at baseline.

q. PET/CT scan to be completed at 3 months (± 10 days), and 6, 9, 12, 18, 24 and 36 months (± 14 days) after CAR-T cell infusion. Scan at 3 months is to be completed at no sooner than 14 days from the most recent dose of NKTR-255 or placebo. A minimum of 28 days is required from the final dose of NKTR-255 until the month 6 scan. Unscheduled imaging should be performed only with high clinical suspicion, preferably with Medical Monitor consultation. Any suspicion of progression should be confirmed with biopsy.

CCI [redacted]

CCI [redacted]

CCI [redacted]

u. Leukapheresis to be completed before lymphodepletion.

v. Information regarding new anticancer therapy, patient's survival, and secondary malignancy will be collected until the patient withdraws consent or the end of study. This information may be collected over the phone.

w. For treatment decisions at Cycle 2 and beyond, blood draw for the central laboratory may be obtained up to 5 days prior to the scheduled day of treatment. Depending on the turn-around time for each center, the results of these safety laboratory tests may not be available prior to the scheduled treatment. If the results are not available, or, at the discretion of the Investigator, local laboratory results may be used to determine eligibility for retreatment. In all cases, if local laboratory results are used for retreatment decisions, duplicate central laboratory tests must be submitted to the central laboratory.

x. Randomization should take place no more than 1 day prior to the first study drug administration.

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z. See Section 5.6.1.

aa. Long-term follow-up visits should be scheduled at 9, 12, 18, 24 and 36 months (±14 days) after CAR-T cell therapy. After the 36-month follow-up, annual survival follow-up (± 1 month) will include collection of subsequent anticancer therapies, survival, and secondary malignancy information and will continue until patient withdraws consent or the end of study; this information may be collected over the phone. If a patient discontinues study treatment and the 30-day safety follow-up is conducted prior to 6-months post CAR-T cell infusion, a long-term follow-up visit at 6 months (± 14 days) after CAR-T cell therapy should be conducted. CCI [redacted]


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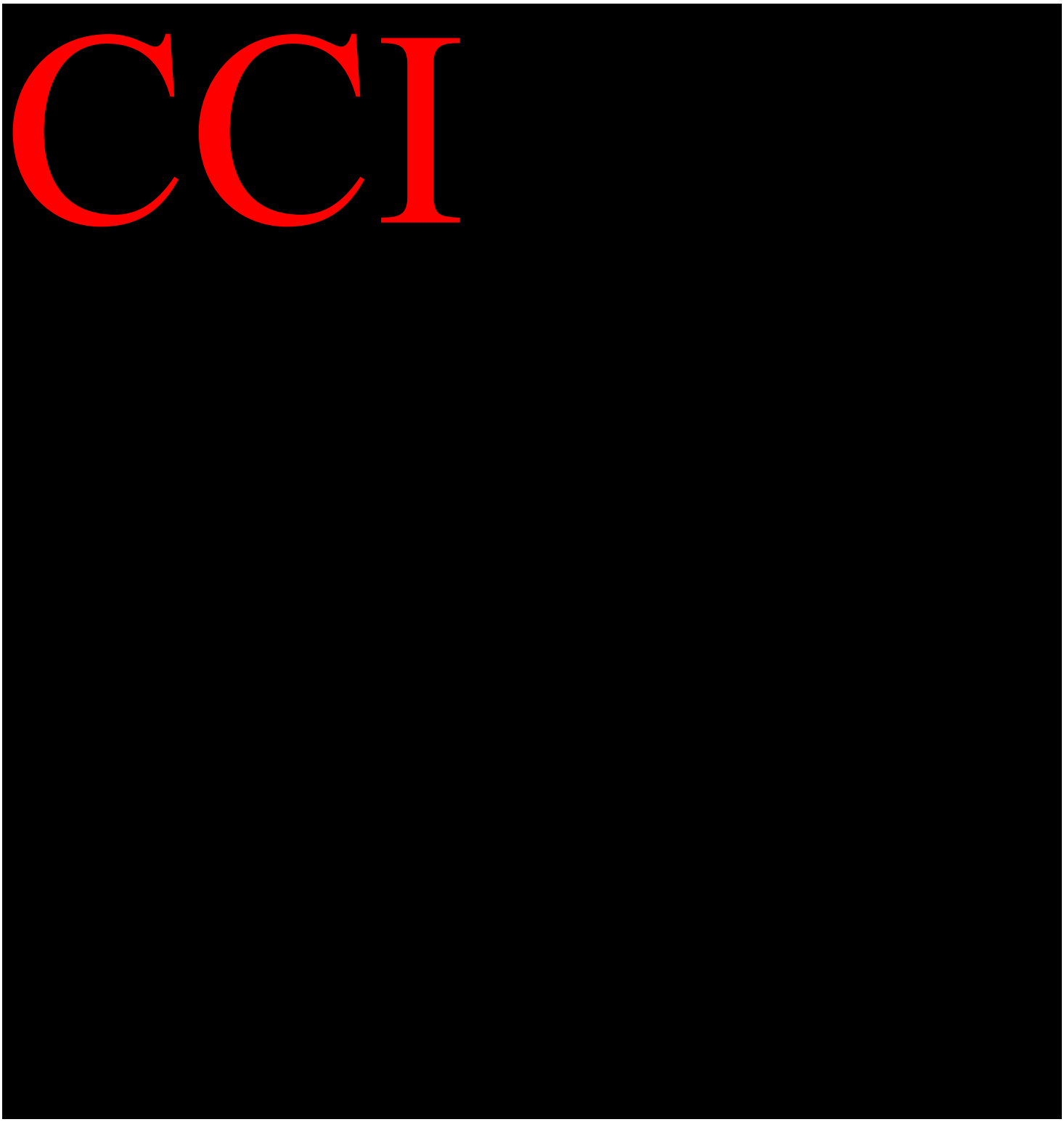

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2.0 INTRODUCTION

2.1 Background

Non-Hodgkin lymphoma (NHL) is one of the most common cancers in the United States (US); in 2022, the American Cancer Society (ACS) estimates 80,470 people will be diagnosed with NHL and 20,250 people will die from this disease (ACS 2022). Diffuse large B-cell lymphoma (DLBCL) is the most common histologic type of NHL, accounting for up to 33% of patients with NHL (National Cancer Institute [NCI] 2022). Although most patients with DLBCL treated in the immunochemotherapy era respond to treatment, about half of patients will either fail to achieve remission or they will relapse (Maurer 2014). In SCHOLAR-1, an international, multicohort retrospective study, 636 patients with refractory DLBCL, defined as progressive or stable disease as best response to chemotherapy and/or relapse ≤ 12 months after autologous stem cell transplant, had poor outcomes with standard salvage therapies, with an objective response rate (ORR) and complete response (CR) rate of 26% and 7%, respectively. The median overall survival (OS) from start of salvage therapy was only 6.3 months (Crump 2017). Recent advances with chimeric antigen receptor-T (CAR-T) cell immunotherapies have improved outcomes of patients with relapsed or refractory (R/R) DLBCL (Locke 2022; Schuster 2019; Abramson 2020).

2.1.1 CAR-T Cell Therapies

T-cells (CD4+/CD8+ T-lymphocytes) engineered to express chimeric antigen receptor (CAR) by gene transfer technology are capable of specifically recognizing their target antigen through the single-chain variable fragment binding domain, resulting in CAR-T cell induced cytotoxicity in a major histocompatibility complex-independent manner (Song 2011). In the past several years, clinical trials from several institutions to evaluate CAR-T cell therapy for B-cell malignancies including B-cell acute lymphoblastic leukemia (B-ALL), B-cell NHL, chronic lymphocytic leukemia, and Hodgkin's lymphoma have demonstrated promising outcomes by targeting CD19 (June 2018), CD20 (Till 2012), or CD30 (Ramos 2017). The most compelling success has been achieved in CD19-specific CAR-T cells for B-ALL with high CR rates of 70% to approximately 94%.

Lymphodepletion chemotherapy followed by infusion of autologous T cells engineered to express a CD19 CAR has shown promising efficacy in patients with R/R large B-cell lymphoma (LBCL). Three CD19-directed CAR-T cell products are currently approved by the US Food and Drug Administration (FDA) for patients with R/R LBCL: axicabtagene ciloleucel (axi-cel; Yescarta® PI), tisagenlecleucel (tisa-cel; Kymriah® PI), and lisocabtagene maraleucel (liso-cel; Breyanzi® PI).

The different CAR-T cell products to date only vary in the construct of the chimeric antigen receptor transfected in the CD4+/CD8+ T-lymphocytes isolated from the individual patients. The antigen targeted may be cancer specific such as CD19, CD20, or B-cell maturation antigen in hematologic malignancies. The development of future generation of CAR-T cells include co-stimulatory domains, like CD28 and/or 4-1BB (CD137), improving proliferation, cytokine secretion, resistance to apoptosis, and *in vivo* persistence. Furthermore, to enhance the safety of

CAR-T cell therapy, so-called smart T-cells, which are either equipped with a suicide gene or include synthetic control devices, are in development (Hartmann 2017).



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Recipient leukocyte depletion by radiation therapy or chemotherapy enhanced the anti-tumor activity of adoptively transferred T-cells in multiple murine models and most clinical trials of adoptive T-cell therapy include chemotherapy before T-cell infusions. In mice, one way that recipient lymphocyte depletion enhances the anti-tumor activity of adoptively transferred T-cells is by increasing serum levels of cytokines such as interleukin (IL)-15. IL-15 is a glycoprotein in the 4-α-helix bundle family of cytokines. IL-15 is primarily produced by dendritic cells, monocytes, and macrophages, and it induces T-cell proliferation and enhances T-cell function.

2.1.1.1 CAR-T Cell Manufacturing Background

In this study, standard lymphodepleting chemotherapy will be administered to patients prior to the T-cell infusion to reduce tumor burden, minimize the risk of tumor lysis syndrome (TLS), and induce lymphopenia to improve CAR-T cell persistence. Clinical trials of T-cell therapy for melanoma at the National Cancer Institute (NCI) have demonstrated that administering lymphodepleting chemotherapy such as fludarabine and cyclophosphamide, or fludarabine, cyclophosphamide, and total body irradiation, prior to the transfer of 10^{10} to 10^{11} polyclonal melanoma-specific T-cells improved the survival of a subset of the transferred T-cells and anti-tumor efficacy (Dudley 2002; Dudley 2005; Dudley 2008). The size of the T-cell pool is subject to homeostatic regulation, and the induction of lymphopenia results in less competition for cytokines such as IL-15 and IL-7 that promote lymphocyte proliferation and survival, and thus leads to the proliferation of residual T-cells including those that are adoptively transferred. Lymphodepleting chemotherapy may also eliminate $CD4^+$ $CD25^+$ regulatory T-cells and activate antigen-presenting cells that may promote the function of transferred T-cells. Studies in murine models subsequently confirmed the human data indicating that lymphodepletion improves the persistence and anti-tumor efficacy of transferred effector T-cells (Wrzesinski 2007).

Substantial data have been presented for patients treated with three different targeted CAR-T cell products; however, there is no consensus on the optimal lymphodepleting chemotherapy regimen to use. Encouraging anti-tumor activity has been observed in 11 patients with NHL who received lymphodepleting chemotherapy with a combination of high doses of cyclophosphamide (60 to 120 mg/kg) and fludarabine (25 mg/m^2/day for 5 days) (Kochenderfer 2015). However, significant cardiac toxicity, neurotoxicity, and death were reported at the highest CAR-T cell dose level (5×10^6 CAR-T cells/kg). When the CAR-T cell dose was reduced to 1×10^6 CAR-T cells/kg and a lower dose regimen of cyclophosphamide (300 mg/m^2/day for 3 days) and fludarabine (30 mg/m^2/day for 3 days) was used, the severe cardiac and neurotoxicity was eliminated, and although transient neurotoxicity (aphasia and ataxia) was still evident, encouraging anti-tumor activity was still observed (Kochenderfer 2014).

2.1.2 NKTR-255

NKTR-255 is a novel immunotherapeutic anticancer drug CCI [redacted]

2.1.2.1 Background on IL-15

As the field of immuno-oncology continues to evolve, research on IL-15 as an immunotherapy has grown and new approaches have facilitated the rational development of IL-15-based therapies to enhance antitumor responses. IL-15 signaling has been shown in pre-clinical models and in early clinical trials to stimulate an array of downstream pathways in immune cells leading to increased cellular growth, decreased apoptosis, and enhanced activation and migration. At endogenous levels, IL-15-mediated responses have been shown to have a crucial role in the development, function, and survival of CD8+ T cells, natural killer (NK) cells, and natural killer T (NKT) cells (Grabstein 1994; Berard 2003; Schluns 2004). Some early clinical successes with IL-15 have validated the concept that stimulating T cell and NK cell responses could yield effective and durable responses in specific cancer types (Margolin 2018; Alderson 2011).

IL-15 is predominantly produced by myeloid cells and signals through a heterotrimeric receptor consisting of the IL-15 receptor (IL-15R) α subunit (IL-15Rα) and IL-2/IL-15R βγ subunits. IL-15Rα is broadly expressed on immune and nonimmune cells. IL-15 binds the membrane-bound IL-15Rα and the complex is presented to the IL-2/IL-15R βγ subunit complex on the same (cis) or adjacent (trans) cell. In addition, IL-15 and membrane-bound IL-15Rα complex can be cleaved from the cell surface and the soluble complex may bind to the IL-2/IL-15R βγ complex. IL-15 exerts its biological effect through these three modes of binding under physiological conditions. Engagement of the IL-2/IL-15R βγ subunit complex can activate Janus kinase (JAK) and signal transducer and activator of transcription 5 (STAT5) signaling (JAK/STAT5) (Robinson 2017). These responses have a crucial role in the development, function, and survival of NK cells and CD8+ T cells; this is reflected by major reductions of NK and CD8+ T cell populations in mice that are genetically deficient in IL-15 or IL-15Rα (Kennedy 2000). In non-human primates, IL-15 delivered exogenously at supra-physiological levels induces the preferential activation and proliferation in CD8+ T cells and NK cells, which have a potential to mediate antitumor responses (Berger 2009).

2.1.2.2 NKTR-255 Mechanism of Action

The NKTR-255 molecule was designed to optimally engage with all known IL-15R-binding receptors, including the IL-15Rα/IL-2Rβγ complex, to achieve extended exposure and sustainable activation of the IL-15 pathway, and thus overcome the challenges of rhIL-15 therapy. Optimal engagement with the IL-15 pathway by NKTR-255 is driven by an extended half-life ($t_{1/2}$) (Kuo 2017) and an IL-15Rα-binding preference. It is anticipated that such optimal engagement can enhance formation of long-term immunologic memory, and lead to antitumor immune responses, without the need for daily dosing (Shah 2021).

IL-15 expression in patients have shown to improve CAR-T cell persistence and specific anti-tumor activity (Kochenderfer 2017). The combination of NKTR-255 and CAR-T cell-based therapies could address the challenges observed with the current CAR-T cell therapies leading ultimately to higher rate of durable response. CCI

[redacted]

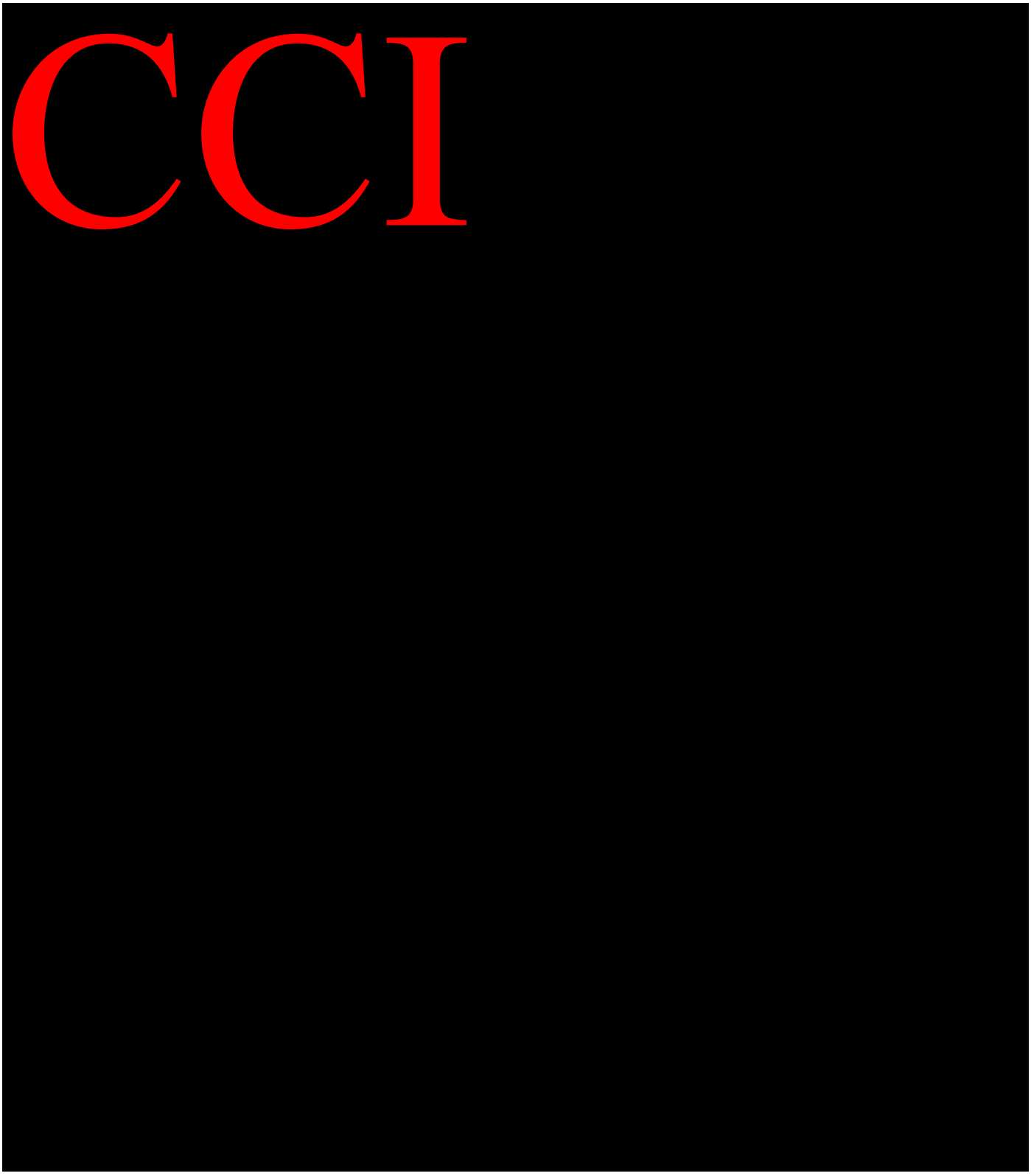
2.1.2.3 NKTR-255 Nonclinical Experience

To characterize NKTR-255 in vitro and in vivo, nonclinical pharmacology, pharmacokinetic (PK), and toxicology/toxicokinetic studies have been conducted.

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3.0 OBJECTIVES

The primary, secondary, CCI objectives for Stage 1 CCI are presented in Table 9.

Table 9: Primary, Secondary, CCI Objectives for Stage 1 CCI

	Stage 1
Primary Objective(s)	To compare the CR rate by BICR at month 6 of treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.
Secondary Objectives	• To evaluate the safety and tolerability of NKTR-255 vs placebo in patients following treatment with CD19-directed CAR-T cell therapy. • To compare the CR rate by BICR at month 3, the ORR by BICR at month 3 and 6, best CR rate and ORR following treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy. • To compare DOR and PFS by BICR, EFS[a] and OS following treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.

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Table 9: Primary, Secondary, CCI Objectives for Stage 1 CCI (Contd)

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BICR = blinded independent central review; CAR-T cell = chimeric antigen receptor T cell;
CR = complete response; CCI DOR = duration of response;
EFS = event-free survival; CCI ORR = objective response rate;
OS = overall survival; CCI PFS = progression free survival; CCI

a. Event-free survival is defined as the time from randomization to the earliest date of disease progression by BICR per Lugano Classification, commencement of new lymphoma therapy, or death from any cause.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria (Stages 1 and 2)

Within the Screening Period and, unless noted otherwise, prior to leukapheresis, patients must meet all the following criteria to be randomized in this study. Informed consent must be signed prior to any study-specific procedures.

1) Male or female ≥ 18 years of age at the time of consent.
2) Received standard of care therapy with axi-cel or liso-cel CCI [redacted] for the respective FDA (or Summary of Product Characteristics [SmPC]) approved indication(s):
   a) liso-cel: Patients with LBCL (including diffuse LBCL [DLBCL] not otherwise specified [including DLBCL arising from indolent lymphoma], high-grade B-cell lymphoma, primary mediastinal LBCL, and follicular lymphoma Grade 3B), who have:
      (1) refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy;
      (2) 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,
      (3) relapsed or refractory disease after two or more lines of systemic therapy.
   b) axi-cel: For the treatment of adult patients with LBCL that is:
      (1) refractory to first-line chemoimmunotherapy;
      (2) relapses within 12 months of first-line chemoimmunotherapy; or
      (3) R/R LBCL after 2 lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal LBLC, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

CCI [redacted]

3) Received lymphodepleting chemotherapy regimen according to the respective FDA (or SmPC) label for CAR-T cell therapy.
4) Fluorodeoxyglucose (FDG)-avid disease on positron emission tomography (PET) imaging within 30 days prior to CAR-T cell infusion.
5) FDG avid lesion(s) on PET/computed tomography (CT) scan following bridging therapy and prior to lymphodepletion, where applicable.
6) Evidence of CD19 expression on any prior or current NHL tumor specimen or a high likelihood of CD19 expression based on disease histology per investigator's assessment.

7) Within 7 days prior to leukapheresis, patient should have an Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 (Appendix 3).

8) Regarding prior systemic anti-tumor therapy:

   a) At least 3 months have elapsed since systemic immune checkpoint inhibitory/immune stimulatory therapy (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc).

   b) At least 2 weeks have elapsed since other prior systemic antitumor therapy.

   c) Bridging therapy (including steroids) is permitted between leukapheresis and lymphodepletion as long as Exclusion Criterion 1 is satisfied.

9) Adequate organ function, defined as:

   a) Adequate bone marrow function (prior to lymphodepletion) for lymphodepletion chemotherapy defined as: absolute neutrophil count (ANC) $\geq$ 1000 cells/mm^3, platelets $\geq$ 50,000 cells/mm^3, and hemoglobin $\geq$ 8 g/dL in the absence of bone marrow involvement by lymphoma. No transfusion within 3 days of bone marrow function assessment; growth factor support is allowed as per institutional practice.

   b) Calculated creatinine clearance (Cockcroft/Gault) > 30 mL/min (Appendix 4).

   c) ALT and AST $\leq$ 3 × upper limit of normal (ULN; or < 5 × ULN for patients with lymphomatous infiltration of the liver) and total bilirubin $\leq$ 2 × ULN (or < 3.0 × ULN for patients with Gilbert's syndrome or lymphomatous infiltration of the liver).

   d) Adequate pulmonary function, oxygen saturation on room air (SaO_2) $\geq$ 92%. Patients with a history of interstitial lung disease should undergo pulmonary function testing and must have a forced expiratory volume in 1 second (FEV_1) of $\geq$ 50% of predicted value or diffusing capacity of the lung for carbon monoxide (DLCO; corrected) $\geq$ 40% of predicted value.

   e) Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) $\geq$ 40% as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition (MUGA) within 60 days before randomization.

10) ECG demonstrating Fridericia's corrected QT interval (QTcF) < 470 ms. Patients with QTcF $\geq$ 470 ms will require clearance by a local cardiologist.

11) Women of reproductive potential (defined as all women physiologically capable of becoming pregnant) must agree to use suitable methods of contraception from the start of study treatment until 1 month after the last dose of study drug (Appendix 6).

12) Males who have partners of reproductive potential must agree to use an effective barrier contraceptive method from the start of study treatment until 1 month after the last dose of study drug.

13) Ability to understand and provide written informed consent.

14) Able and willing to comply with study visit schedule and procedures, including tumor biopsy where accessible.

Additional Eligibility Criteria Following CD19 Targeted CAR-T Cell Infusion (Stages 1 and 2):

Patients who have received commercially released CAR-T cell infusion must satisfy the following criteria on the day of randomization:

15) No fever ≥ 38.0°C/Grade ≥ 1 CRS (American Society for Transplant and Cellular Therapy [ASTCT] criteria [Lee 2019]) within 24 hours.

16) No Grade ≥ 3 CRS (ASTCT criteria) within 72 hours.

17) No previous Grade ≥ 3 immune effector cell-associated neurotoxicity syndrome (ICANS) of > 72 hours duration.

18) No Grade ≥ 2 ICANS (ASTCT criteria).

19) No tocilizumab and/or dexamethasone within 48 hours.

20) No active, serious, and/or uncontrolled infection(s).

21) No other contraindication according to the Investigator's assessment.

22) Patients must satisfy the following laboratory test results:

- ANC or absolute granulocyte count (AGC) ≥ 1000/µL
- Platelets ≥ 30,000/µL
- Hemoglobin ≥ 8 g/dL
- Leukocytes ≥ 3000/µL

Randomization should occur no more than 1 day before the first study drug infusion.

4.2 Exclusion Criteria (Stages 1 and 2)

1) Use of therapeutic doses of corticosteroids (≥ 5 mg/day prednisone or equivalent) or other systemic immunosuppression within 7 days prior to leukapheresis or within 72 hours prior to CAR-T cell infusion. Topical and/or inhaled steroids are permitted.

2) Prior treatment with any CD19-directed CAR-T cell therapy other than the treatment planned per Inclusion Criterion 2.

3) For allogeneic hematopoietic cell transplant recipients, active graft versus host disease (GVHD) and/or systemic GVHD therapy during screening or up to 30 days prior to leukapheresis.

4) Known active hepatitis B (detectable hepatitis B DNA) or hepatitis C (detectable hepatitis C RNA).

5) Known human immunodeficiency virus (HIV) infection.
6) Pregnant or breastfeeding women.
7) Prior treatment with any IL-2 or IL-15 agonist and/or biosimilar agents.
8) Active autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, ulcerative colitis, Crohn's disease], celiac disease, or other serious chronic gastrointestinal conditions associated with diarrhea, autoimmune vasculitis, systemic lupus erythematosus, Wegener syndrome [granulomatosis with polyangiitis], myasthenia gravis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.) within 1 year prior to randomization. The following are exceptions to this criterion:
    a) Vitiligo
    b) Alopecia
    c) Hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
    d) Type 1 diabetes mellitus
    e) Psoriasis not requiring systemic treatment
    f) Conditions considered to be low risk of serious deterioration by the Investigator and with Medical Monitor approval
9) History of any one of the following cardiovascular conditions within the 6 months prior to randomization: class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, or unstable angina; unless clearance by a cardiologist is obtained. 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.
10) History or presence of clinically relevant central nervous system (CNS) pathology, such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, or psychosis that in the opinion of the Investigator is a contraindication to study treatment.
11) History of CNS lymphoma, primary CNS lymphoma, brain metastases, or detectable malignant cells in the cerebrospinal fluid.
12) History of solid organ transplantation.
13) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Medical Monitor.
14) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted.

15) Active or current participation on any other interventional studies.

16) Use of an investigational agent or an investigational device within 28 days of CAR-T cell therapy.

17) Live, attenuated vaccines are prohibited within 30 days of randomization.

18) Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of results.



5.0 TREATMENT PLAN

5.1 Overview

This is a Phase 2/3, multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of NKTR-255 following CD19-directed CAR-T cell therapy. Patients will be treated with a lymphodepletion chemotherapy regimen (consistent with the Principal Investigator-selected CD19-directed CAR-T cell therapy) prior to CD19-directed CAR-T cell infusion, as per label. The study is conducted in two stages, with routine safety monitoring being conducted by the Data Monitoring Committee (DMC) on a regular basis

- In **Stage 1** (Phase 2), patients with R/R LBCL who have been treated with commercial CAR-T cell therapy will be randomized CCI to receive either 1.5 µg/kg NKTR-255, 3.0 µg/kg NKTR-255, a step-up dose regimen initiating with 3.0 µg/kg NKTR-255 in Cycle 1 (C1) and continuing in Cycle 2 and subsequent cycles (C2+) with 6.0 µg/kg NKTR-255 (hereinafter referred to as 3.0/6.0 µg/kg NKTR-255), or placebo. CCI

  Randomization will be stratified according to:

  - The cellular product that the patient receives CCI
  - Baseline lactate dehydrogenase (LDH) (defined as LDH ≥ 440 U/L or < 440 U/L [Rabinovich 2021] prior to lymphodepletion confirmed by central laboratory)

  Once patients meet criteria for study drug administration, patients will be treated with study drug (ie, NKTR-255 at 1.5, 3.0, or 3.0/6.0 µg/kg, or placebo) given by IV infusion. Thereafter, study drug will be administered q3w for up to 7 cycles or 5 months, whichever is earlier. The last dose of study drug is to be given at least 28 days before the PET/CT scan conducted at 6 months post CAR-T cell infusion.

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The DMC will review all available safety, CCI data after approximately CCI patients have completed 2 cycles of study drug treatment. CCI Additionally, cohort dose

optimization (including C1) or closure of any cohorts may occur based on safety, CCI data review.

An enrollment pause will be implemented at the end of Stage 1 CCI , and the DMC will review safety and efficacy data from all available cohorts to make go/no-go and dose selection recommendations CCI . The study team will be unblinded at the end of Stage 1 to review the totality of the data including efficacy, safety, CCI data before the study proceeds CCI .



All procedures are outlined in the Schedule of Events (Section 1.2).

5.2 Study Periods

5.2.1 Screening Period

Patients will provide written informed consent to participate in the study. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (eg, full physical exam) as long as the procedures were completed within the protocol defined window. After signing the ICF, patients will be evaluated for entry criteria during the screening period before administration of study drug(s). Rescreening after screen failure will be

allowed, as long as the outer limit of C1D1 dosing has not passed, ie, 21 days after CAR-T cell infusion.

Patients deemed eligible to receive CAR-T cell therapy may be consented prior to leukapheresis for CAR-T cell manufacturing, but should be consented prior to lymphodepletion. Patients will undergo lymphodepletion chemotherapy as recommended by the CAR-T cell manufacturer and soon after will receive a one-time CD19-directed CAR-T cell infusion as directed by the respective product label. Pretreatment evaluations should be conducted according to Schedule of Events (Section 1.2) prior to receiving lymphodepleting chemotherapy. Where possible, some of the evaluations should be completed per standard of care.

Subsequently, eligibility will be reassessed following CD19-directed CAR-T cell infusion and prior to randomization.

5.2.2 Assigning Patient Numbers

Each patient will be assigned a unique patient number after signing the ICF. Patient numbers will be used on all patients' study information. Patient numbers will not be reassigned.

5.2.3 Randomization and Stratification

Patients who received CD19-directed CAR-T cell therapy and satisfy the additional eligibility criteria will be randomly assigned to receive NKTR-255 or placebo as follows:

- Stage 1: patients will be randomized CCI [redacted] to 1.5 µg/kg NKTR-255, 3.0 µg/kg NKTR-255, 3.0/6.0 µg/kg NKTR-255, or placebo.

CCI [redacted]

In both stages, patients will be stratified as follows:

- The cellular product that the patient receives CCI [redacted].
- Baseline LDH (defined as LDH ≥ 440 U/L or < 440 U/L prior to lymphodepletion confirmed by central laboratory)

The randomizations CCI [redacted] will take place no more than 1 day prior to the first study drug administration.

5.2.4 Treatment Period

Start of treatment is defined from the first dose of study drug. Patients will be treated up to 7 cycles or 5 months, whichever is earlier, or until disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, patient decision to discontinue treatment or withdraw consent, loss to follow-up, or Nektar Therapeutics

decides to terminate the trial, whichever is sooner. The last dose of study drug is to be given at least 28 days before the PET/CT scan conducted at 6 months post CAR-T cell infusion. Study treatment with initial follow-up is expected to be approximately 12 months.

5.2.5 Replacement of Study Patients

Patients who do not meet eligibility criteria are considered as screen failures and will not proceed to randomization. CCI [redacted]

5.2.6 End of Treatment

Patients may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment. End of Treatment (EOT) is to be performed after study treatment is discontinued, or before a new antineoplastic regimen has been initiated. Discontinued reasons for EOT are:

- Radiographic disease progression as determined by the Investigator.
- Nonresolution of unacceptable AEs.
- Symptomatic deterioration.
- Noncompliance of the patient with protocol-mandated procedures based on the judgment and agreement of both the Investigator and Sponsor.
- Continued participation is no longer in the patient's best interest in the opinion of the Investigator.
- If a female patient becomes pregnant, administration of the study drug(s) must be discontinued immediately.
- Withdrawal of consent.
- The study is terminated by the Sponsor.
- Completion of planned study drug treatment period (approximately 5 months).
- Patient meets any of the criteria for permanent discontinuation of study drug (see Section 5.4)

In the event of a patient's withdrawal of consent, the Investigator should promptly notify the Sponsor.

5.2.7 Safety Follow-up Evaluations

Safety follow-up is to be performed at 30 days + 3 days after the last dose of study treatment; procedures are specified in the Schedule of Events (Section 1.2).

In case of an AE or SAE, the patient will be followed for safety as described in Section 7.5 and Section 7.8, respectively.

5.2.8 Long-term Follow-up

Long-term follow-up visits should be scheduled at 9, 12, 18, 24 and 36 months (±14 days) after CAR-T cell therapy. After the 36-month follow-up, annual survival follow-up (± 1 month) will include collection of subsequent anticancer therapies, survival, and secondary malignancy information and will continue until patient withdraws consent or the end of study; this information may be collected over the phone. If a patient discontinues study treatment and the 30-day safety follow-up is conducted prior to 6-months post CAR-T cell infusion, a long-term follow-up visit at 6 months (± 14 days) after CAR-T cell therapy should be conducted. All procedures are outlined in the Schedule of Events (Section 1.2).

PET/CT scans will be collected at 18, 24 and 36 months.

Patients will be followed long term until disease progression, the patient dies, is lost to follow-up, withdraws consent, starts a new anti-cancer therapy, or Sponsor decides to discontinue the study.

5.2.9 End of Study

End of study is defined as no more than 5 years after the last patient received his or her first dose of study drug or Sponsor decision to terminate the study, whichever comes first.

5.3 Administration of Study Drug

5.3.1 Study Drug Dosing

NKTR-255 or placebo will be administered as a 30-minute (± 5 minutes) infusion q3w, with the first dose being given approximately 14 days after CAR-T cell infusion. Additional dosing criteria will be assessed prior to the first and subsequent study drug infusions (see Section 4.3). Each patient's study drug dose will be determined by the patient's weight in kilograms, which will be determined on the day of each dosing. See Section 5.6.1 for premedication requirements.

5.3.1.1 Study Drug Dose Delay and Adjustment Criteria

5.3.1.1.1 Dose Delay

Patients will be assessed prior to each study drug infusion to determine if they fulfill the requirements for study drug infusion (Section 4.3). Dosing after the first cycle may be delayed for up to 3 weeks at the discretion of the Investigator with the approval of the Medical Monitor to manage toxicities or untoward medical events.

5.3.1.1.2 Dose Adjustment

Dose adjustments are permitted for study drug. Dose adjustments must be approved by the Medical Monitor.

Per recommendation of the Investigator and approval of the Sponsor's Medical Monitor, study drug may be reduced by 50% based on observed toxicities as shown in Table 10. If the study drug dose is reduced, the dose level should remain at this level throughout the remainder of the study and cannot be re-escalated.

Tumor and radiographic assessments should continue as per protocol even if dosing is stopped or delayed, and patients must otherwise meet the criteria for continued treatment at the time re-initiation of study therapy is considered. Toxicities should be managed as described in Section 5.7.

Table 10: Recommended Dose Modifications for Related Adverse Reactions

Adverse Reaction and Severity	Dose Modification
Grade 4 CRS of any duration or Grade 3 CRS that does not resolve to Grade ≤ 2 within 72 hours	Permanently discontinue study drug
Grade 4 non-hematological toxicity that is not considered by the Investigator to be attributable to another identifiable cause	
Hematologic toxicity as follows: • Grade 4 hematologic toxicity lasting > 7 days (excluding lymphopenia and B-cell aplasia) • Grade ≥3 thrombocytopenia with bleeding • Febrile neutropenia lasting >48 hours	
Grade ≥ 3 infusion-related reaction to study drug infusion that does not resolve to Grade ≤ 2 within 4 hours	
Grade ≥ 3 ICANS of greater than 3 days duration	
If more than one seizure occurs	
Grade ≥ 3 hemophagocytic lyphohistiocytosis/ macrophage activation syndrome (HLH/MAS)	
Any Grade ≥ 3 AST, ALT, and bilirubin elevation ≥ 7 days	
Grade 3 non-hematologic toxicity (other than as noted above)	Study drug may be withheld if toxicity cannot be managed by adequate medical intervention. Study drug dosing may resume at a lower dose level when toxicity resolves to Grade 1 or returns to baseline, except for instances where the potential recurrence of the event poses an undue risk for the patient
Grade 1 or 2 toxicity (other than as noted above)	No requirement for dose delay or dose reduction. If the toxicity persists at Grade 2, a dose delay or dose reduction may be implemented at the discretion of the Investigator with the approval of the Medical Monitor.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; ULN = upper limit of normal

5.3.1.2 Criteria to Resume Study Drug

Patients will be permitted to resume study drug following resolution of the AE to Grade ≤ 1 or to baseline within 2 weeks after the completion of the prior cycle, with the exception of patients who meet criteria for permanent discontinuation as specified in Section 5.4. Patients who meet criteria for permanent discontinuation must not receive further study drug.

Following a decision to resume study drug dosing, the patient should restart treatment when the criteria are met, but no earlier than 21 days following the prior dose of study drug.

Patients may resume treatment when the study drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT **or** total bilirubin.

5.3.2 Criteria to Pause Enrollment

5.3.2.1 Stage 1

Enrollment will be paused at Sponsor's discretion or if any of the following criteria are met:

1) Incidence of Grade 5 NKTR-255-related AEs is > 5% overall

OR

2) Incidence of Grade 3 or higher NKTR-255-related non-hematologic AEs lasting more than 7 days is > 33% overall

If either of these criteria are met, an ad-hoc meeting of the DMC will be held to review data by cohort and determine whether the study or selected dose-level cohort will continue or will continue with modification.

As applicable to the above criteria, "related" is defined as in Section 7.4, ie, "*There is a reasonable possibility that the AE is caused by the study drug(s). A plausible temporal sequence exists between the time of administration of the study drug(s) and the development of the AE. The AE cannot be reasonably explained by the known characteristics of the patient's clinical state or other concomitant therapies or interventions administered to the patient*."

The incidence rates will be calculated by the Independent Statistical Center (ISC), which is an external group of statisticians and statistical programmers selected to facilitate the activities of the DMC. The calculated incidence rates as well as SAE listings and suspected unexpected

serious adverse reactions (SUSARs) will be sent to DMC for review on a monthly basis in addition to the regularly scheduled DMC safety review meetings.



5.4 Permanent Treatment Discontinuation Criteria

Patients meeting any of the criteria for permanent discontinuation of study drug listed in Table 10 or in Section 5.7.8 will be required to permanently discontinue study drug(s).

Tumor and radiographic assessments should continue as per protocol even if dosing is delayed, and patients must otherwise meet the criteria for continued treatment at the time re-initiation of study therapy is considered. Toxicities should be managed as described in Section 5.7.

Patients who receive study drug and are subsequently discontinued from receiving further study treatment (eg, due to toxicity) will remain on study and continue to have all scheduled follow-up evaluations per the schedule of events (see Section 1.2). Patients will be followed long term as described in Section 5.2.8. All patients who receive treatment with study drug should be followed for safety at least 30 days after the last dose of study drug or until a new antitumor therapy has been initiated, whichever comes earlier.

5.5 Study Stopping

Throughout the study CCI , the DMC will perform routine safety monitoring approximately every 6 months in addition to the scheduled safety evaluation in Stage 1, safety and efficacy evaluation at the end of Stage 1 CCI . Additionally, when any safety criterion to pause enrollment is met (see Section 5.3.2), or any signal of potential safety concern emerges based on the monthly (Stage 1) CCI safety reports an ad-hoc DMC will be convened. CCI

CCI [redacted]

5.6 Prior and Concomitant Medications

All prescription and over-the-counter (OTC) medications (excluding vitamin and mineral supplements and herbal medications, unless used to treat an AE) taken by the patient will be documented through 30 days after last dose of NKTR-255. In addition, any IV immunoglobulin (IVIG) treatment will be documented through the 12-month follow-up period. Start and stop date, dose and route of administration, frequency, and indication should be recorded.

As a cytokine modulator, NKTR-255 has the potential to affect the PK of co-administered drugs whose elimination is mainly through CYP-mediated metabolism. Although this drug-drug interaction risk is considered low given increases of cytokines resulting from NKTR-255 in Study 18-255-02 was modest and transient (returning to baseline around Day 2 to 3), drugs with a narrow therapeutic index or sensitive substrates of CYP450 should be avoided in Stage 1 and should be closely monitored for safety events when these drugs are used concomitantly CCI [redacted].

In addition, subsequent anti-cancer therapies in the long term follow-up period should also be documented and recorded.

5.6.1 Permitted and Pre-Medications

Premedication with antihistamine (H1 receptor blocker such as diphenhydramine 25 mg either orally [PO] or IV equivalent) and with acetaminophen (500-650mg PO or equivalent) must be administered approximately 30 to 60 minutes prior to each infusion of NKTR-255/placebo.

The following are permitted as described:

- Treatment for flu-like symptoms with acetaminophen (paracetamol) is permitted per the Investigator's discretion.
- Treatment for flu-like symptoms with antihistamines is permitted per the Investigator's discretion.
- If a patient reports symptoms (such as nausea and/or vomiting), prophylactic anti-emetics may be used in subsequent cycles.
- Intravenous immunoglobulin replacement is permitted for clinically significant hypogammaglobulinemia (eg, systemic infection) according to local guidelines.
- Use of tocilizumab is permitted per usage described in Table 12.
- Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). A brief (less than 3 weeks) course of

corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

- Therapeutic doses of steroids must be stopped > 72 hours prior to leukapheresis and > 48 hours prior to CAR-T cell infusion; physiological replacement doses of 5 mg/day prednisone or equivalent are allowed.
- Consider G-CSF 5 μg/kg/day if/when ANC < 500 cells/mm^3 per institutional standards.
- All vaccines against SARS-CoV-2 are acceptable.

5.6.2 Prohibited Medications

The following medications are prohibited during administration of study drug:

- Immunosuppressive agents, including disease-modifying anti-rheumatic drugs (eg, anti-TNF)
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.6.1)
- Any antineoplastic therapy other than those specified (ie, chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, investigational agent or therapy) is prohibited during the study.
- Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after CAR-T cell administration unless used to manage CAR-T cell therapy related toxicities. Other medications that might interfere with the evaluation of CAR-T cell therapy, such as non-steroidal anti-inflammatory agents should also be avoided for the same period unless medically necessary.
- Consideration should be given to withholding antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (eg, alpha blockers for benign prostatic hypertrophy), prior to each study drug infusion, particularly when therapy involves multiple antihypertensive drugs and classes other than thiazide diuretics. Antihypertensive medications should be withheld no less than 12 hours and no more than 48 hours prior to each study drug infusion. Antihypertensive medications may be reinstituted in between study drug infusions if the diastolic pressure exceeds 90 mmHg and/or the systolic pressure exceeds 160 mmHg.
- Investigators should follow their institutional guidelines for discontinuation of anti-coagulant therapy (eg, aspirin and Plavix) before infusions. Investigators should understand current best-practice recommendations for pre- and post-procedure management of antithrombotic therapy, balancing the risk/benefit of modifying antithrombotic therapy in patients.
- Live, attenuated vaccines are prohibited within 30 days before the first dose of study drug and during the treatment period of the study. Note: Acceptable vaccines include killed vaccines.

- Information on pretreatment and prohibited medications can be found in the respective product labels: YESCARTA® PI, BREYANZI® PI, and KYMRIAH® PI.
- No G-CSF allowed earlier than 2 days post CAR-T cell infusion
- Granulocyte-macrophage colony-stimulating factor is not allowed at any time during the treatment period.
- Any investigational agent or an investigational device, other than NKTR-255.

5.7 Potential Risks and Toxicities

The mechanism of action of NKTR-255 involves the activation of T cells and NK cells; therefore, a spectrum of events involving IRRs, target-mediated cytokine release, and/or hypersensitivity reaction may occur. These reactions may be allergic or non-allergic in nature and may be associated with the release of cytokines (eg, IL-6 and IFN-γ) into the blood from immune cells affected by the immunotherapy.

Administration of NKTR-255 is expected to enhance the persistence and activity of CAR-T cell therapy. Similarly, cytokines released in response to CAR-T cell infusion may activate endogenous T cells and/or other immune effector cells, thus potentiating the immune-related AEs associated with interleukin therapies such as NKTR-255. Thus, administration of the two agents in combination could exacerbate the AEs expected from each agent alone.

A summary of potential risks and management of treatment toxicities is provided Section 5.7.1 through Section 5.7.9.

5.7.1 Infusion-related Reactions/Hypersensitivity Reactions

An IRR may occur during or after IV administration of biologics and therapeutic proteins, including NKTR-255. It clinically manifests as chills/rigors, fever, headache, pruritus, rash, arthralgia, myalgia, bronchospasm, hypotension, and other hypersensitivity/allergic-like reactions. The IRRs may be clinically similar to manifestations of cytokine-related toxicities and CRS, but occur shortly after the start of IV administration (time to onset ranged from a few minutes to around 1-2 days after start of IV administration) (Lee 2014; Lee 2019). Infusion reactions should be graded as described in Table 11.

Treatment recommendations are provided in Table 11 and may be modified based on local treatment standards and guidelines, as appropriate.

Table 11: Management of Infusion-related Reactions/Hypersensitivity Reactions

Grade	Symptoms	Management
1	Mild reaction; infusion interruption not indicated; intervention not indicated	Remain at the bedside and monitor the patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before subsequent infusions.
2	Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours	• Stop study drug infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at the bedside and monitor the patient until resolution of symptoms. • Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. • For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before the infusion. If necessary, corticosteroids (up to 25 mg of methylprednisolone or equivalent) may be used.
3 or 4	Severe reaction, Grade 3: prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: life threatening; pressor or ventilator support indicated.	For Grade 3 or Grade 4 symptoms: Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the patient as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. The patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at the bedside and monitor the patient until recovery of the symptoms.

IV = intravenous

Note: In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

5.7.2 Cytokine-Related Toxicities

Cytokine-related toxicity is a recognized consequence of interleukin therapy and could include a broad range of AEs associated with the active cytokines in the blood via the metabolism of NKTR-255 drug product. These toxicities may be characterized by the constellation of signs and symptoms of flu-like symptoms (eg, rigors and chills), fatigue, rash, pruritus, arthralgia, hypotension, and transient elevation of hepatic transaminases, generally coinciding with the time of peak active cytokine concentration in the blood (Romee 2018). Hypotension may need to be

managed with robust hydration, as clinically indicated in accordance with institutional guidelines. To minimize the risk and enhance tolerability, prophylactic use of either acetaminophen or ibuprofen is permitted on study per the Investigator's discretion. Prophylaxis for flu-like symptoms can be initiated on Day 1 of each dosing cycle and may continue as needed (see Section 5.6.1).

5.7.3 Cytokine Release Syndrome

Administration of CAR-T cells may be associated with CRS. CRS may be characterized by high fever, rigors, fatigue, nausea, headache, tachycardia, hypotension, dyspnea, hypoxia, myalgia/ arthralgia, anorexia, coagulation abnormalities, organ dysfunction, and neurologic abnormalities.

In nonclinical tests of NKTR-255, transient elevations in cytokines and cytokine receptors (eg, IL-5, IL-6, IL-10, IL-18, MCP-1, sCD25, sTNFRI, and sTNFRII) were detected after administration of NKTR-255 to monkeys (see Section 2.1.2.3). Clinical experience with NKTR-255 showed that inflammatory cytokines, particularly IFN-γ, MCP-1 and IL-6 were elevated 3-6 hours post NKTR-255 administration. Elevations were transient in nature and rapidly returned to baseline levels by day 2-3, consistent with the observed safety data showing that CRS-related adverse reactions within the first 24 hours were transient and mostly resolved within 24 hours of onset.

If a patient becomes febrile or develops symptoms of CRS, cytokine levels, serum ferritin, C-reactive protein (CRP), coagulation studies, and/or markers of TLS (eg, chemistry, uric acid, LDH) may be measured, and persistence and/or phenotype of the transgene-expressing cells may be evaluated, as clinically indicated.

Any patient who develops clinical evidence of symptoms related to CRS will have a work-up to exclude infection or other causes, as clinically appropriate. Initial treatment should consist of supportive measures as dictated by the clinical and laboratory findings, and may include fluid replacement, medications to support blood pressure, antipyretics, oxygen supplementation, anti-seizure medications, and broad-spectrum antibiotics if infection cannot be excluded as a potential etiology for the signs and symptoms.

Guidelines for management of CRS based on the ASTCT Consensus Grading are provided in Table 12 (Lee 2019). Treatment recommendations found in the package insert. Other cytokine-directed therapies may be considered after discussion with the Principal Investigator.

A treatment algorithm for management of CRS is provided in Table 12, which may be modified based on local treatment standards and guidelines, as appropriate.

Table 12: CRS Consensus Grading and Management

Grade	Symptoms	Suggested Treatment
1	Temperature ≥ 38°C [a]	• Manage symptomatically with acetaminophen prn. • If less than 72 hours after study drug infusion or persistent fever, consider tocilizumab 8 mg/kg IV (max 800 mg in a single dose) in combination with dexamethasone 10 mg IV q24h. • If not on levetiracetam, initiate levetiracetam 500 mg PO BID. • Telemetry monitoring if patient on concurrent ibrutinib or if clinically indicated. • G-CSF to be continued until ANC ≥ 500 cells/mm^3 for 2 consecutive days.
2	• Temperature ≥ 38°C [a] with • Hypotension not requiring vasopressors and/or • Hypoxia requiring O_2 ≤ 6 L/min	• Manage with fluid bolus and oxygen (to keep oxygen sat ≥ 92%) as appropriate. • Tocilizumab 8 mg/kg IV, max 800 mg in a single dose, may repeat q8h if needed, to max of 3 doses in 24 hours and no more than 4 doses total. It is recommended to administer 2 doses of dexamethasone 10 mg IV. First dose is to be given at the time of the first dose of tocilizumab and a second dose of dexamethasone 12 hours later. Additional doses may be clinically indicated. • Non responders to 2 doses of tocilizumab and dexamethasone may require additional anti-cytokine therapy (ie, anakinra). [b] Contact IMTX Outpatient Attending. • If not on levetiracetam, initiate levetiracetam 500mg PO BID. • Telemetry monitoring. • G-CSF to be continued until ANC ≥ 500 cells/mm^3 for 2 consecutive days.
3	• Temperature ≥ 38°C [a] with • Hypotension requiring vasopressor with or without vasopressin and/or • Hypoxia requiring O_2 ≥ 6 L/min by nasal cannula or mask	• Consider ICU transfer. • Tocilizumab 8 mg/kg IV, max 800 mg in a single dose, may repeat q8h if needed, to max of 3 doses in 24 hours and no more than 4 doses total. • Dexamethasone 10 mg IV q6-12h. • Non responders to tocilizumab may require additional anti-cytokine therapy (ie, anakinra). [b] • If not on levetiracetam, initiate levetiracetam 500 mg PO BID. • Telemetry monitoring. • G-CSF to be continued until ANC ≥ 500 cells/mm^3 for 2 consecutive days.

Table 12: CRS Consensus Grading and Management (Contd)

Grade	Symptoms	Suggested Treatment
4	• Temperature ≥ 38°C [a] with • Hypotension requiring multiple vasopressors (excluding vasopressin) and/or • Hypoxia requiring positive pressure ventilation (eg, CPAP, BiPAP, intubation and mechanical ventilation)	• Transfer to/continue ICU care. • Tocilizumab 8 mg/kg IV, max 800 mg in a single dose, may repeat q8h if needed, to max of 3 doses in 24 hours and no more than 4 total doses. • Dexamethasone 10 mg IV q6h. Consider changing to methylprednisolone 1,000 mg IV qd x3d if unstable, not improving or deteriorating. Discuss with IMTX Outpatient Attending. • Non responders to tocilizumab and dexamethasone may require additional anti-cytokine therapy (ie, anakinra). [b] Contact IMTX Outpatient Attending. • Telemetry monitoring. • If not on levetiracetam, initiate levetiracetam 500 mg PO BID. • G-CSF to be continued until ANC ≥ 500 cells/mm^3 for 2 consecutive days.

ANC = absolute neutrophil count; BID = twice a day; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; ICU = intensive care unit; IMTX = immunotherapy; IV = intravenous; PO = per os; q6h = every 6 hours

CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

a. Fever is defined as temperature ≥ 38°C not attributable to any other cause and is required for the diagnosis of CRS. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b. Anakinra (IL-1 receptor antagonist) is to be given subcutaneously 1-8 mg/kg actual weight divided into 2-3 doses in 24 hours. Maximum dose 8 mg/kg in 24 hours. Round to the nearest 100 mg vial size.

Source: Modified from Lee 2019.

5.7.4 ICANS or Neurological Toxicity

ICANS may be manifested by encephalopathy, word finding difficulty or aphasia, dysgraphia, depressed level of consciousness, seizures, motor weakness, focal/diffuse cerebral edema on imaging or signs of raised intracranial pressure. ICANS is usually reversible but can be irreversible or fatal.

Levetiracetam (500 mg bid PO starting dose) or other anti-seizure medication should be considered prophylactically prior to treatment with liso-cel for patients with secondary CNS involvement by malignancy, history of CNS irradiation or other intensive CNS-directed therapy.

Patients experiencing clinical features of ICANS should be evaluated as clinically indicated with brain imaging, lumbar puncture with cerebrospinal fluid evaluation, and Neurology consult.

For patients who develop mild neurologic manifestations (ASTCT Grade 1; Table 13), symptomatic care and levetiracetam are recommended. Discussion with the Principal Investigator or designee is recommended. For patients with worsening neurologic changes, the addition of corticosteroids should be considered (eg, dexamethasone 10 mg IV every 6 to

24 hours). Tocilizumab (4-8 mg/kg IV) or other cytokine-directed therapies may be used if the patient has concurrent CRS.

A treatment algorithm for management of ICANS is provided in Table 13, which may be modified based on local treatment standards and guidelines, as appropriate.

Table 13: ICANS Consensus Grading

Grade	ICE Score[a, b]	Depressed Level of Consciousness[c]	Seizure	Motor Findings[d]	Elevated ICP/ Cerebral Edema	Management
Grade 1	7-9	Awakens spontaneously	N/A	N/A	N/A	• If not on levetiracetam, consider initiating levetiracetam, 500 mg PO BID. • G-CSF to be continued until ANC ≥ 500 cells/mm^3 for 2 consecutive days. • Neurology consult if atypical or unusual features. • Consider cytokine-directed therapy if concurrent CRS. • If less than 72 hours after study drug infusion, consider dexamethasone 10 mg IV q12-24h for 2 to 3 days.
Grade 2	3-6	Awakens to voice	N/A	N/A	N/A	• Dexamethasone 10 mg IV q12h for 2 to 3 days. Consider increase of dexamethasone up to 20 mg IV q6h if unstable, not improving or deteriorating. • If not on levetiracetam, initiate levetiracetam 500 mg PO BID. • G-CSF to be continued until ANC ≥ 500 cells/mm^3 for 2 consecutive days. • Neurology consult if atypical or unusual features. • Consider cytokine-directed therapy if concurrent CRS.
Grade 3	0-2	Awakens only to tactile stimulus	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	N/A	Focal/local edema on neuroimaging[e]	• Consider ICU care. • Dexamethasone 10-20 mg IV q6-12h. • If not on levetiracetam, initiate levetiracetam 500 mg PO BID. • In patients with seizures, consider additional anti-seizure agents. • G-CSF to be continued until ANC ≥ 500 cells/mm^3 for 2 consecutive days. • Neurology consult. • Consider cytokine-directed therapy if concurrent CRS. • If not improving, consider use of other anti-cytokine therapy (ie, anakinra).[f]

Table 13: ICANS Consensus Grading (Contd)

Grade	ICE Score[a, b]	Depressed Level of Consciousness[c]	Seizure	Motor Findings[d]	Elevated ICP/ Cerebral Edema	Management
Grade 4	0 (patient is unarousable and unable to perform ICE)	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between	Deep focal motor weakness such as hemiparesis or paraparesis	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad	• Consider ICU transfer. • Dexamethasone 20 mg IV q6h. • Consider methylprednisolone 1000 mg IV daily for 3 days. • If there is not a rapid response, not improving, unstable, or deteriorating, contact IMTX Outpatient Attending for use of other anti-cytokine therapy (ie, anakinra).[f] • If not on levetiracetam, initiate levetiracetam 500 mg PO BID. • In patients already on levetiracetam, consider additional anti-seizure agents. • G-CSF to be continued until ANC ≥ 500 cells/mm^3 for 2 consecutive days. • Telemetry monitoring. • Consider cytokine-directed therapy if concurrent CRS.

ANC = absolute neutrophil count; BID = twice a day; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; ICU = intensive care unit; IMTX = immunotherapy; N/A = not applicable; PO = per os; q6h = every 6 hours

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

a. ICE Score: **Orientation:** orientation to year, month, city, hospital – 4 points.
Naming: ability to name 3 objects (eg, point to clock, pen, button) – 3 points.
Following commands: ability to follow simple commands (eg, "show me 2 fingers" or "close your eyes and stick out your tongue") – 1 point.
Writing: ability to write a standard sentence (eg, "our national bird is the bald eagle") – 1 point.
Attention: ability to count backwards from 100 by 10 – 1 point.

b. A patient with ICE score = 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with ICE score = 0 may be classified as grade 4 ICANS if unarousable.

c. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

d. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

e. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

f. Anakinra (IL-1 receptor antagonist) is to be given subcutaneously 1-8 mg/kg actual weight divided into 2-3 doses in 24 hours. Maximum dose 8 mg/kg in 24 hours. Round to the nearest 100 mg vial size.

Source: Modified from Lee 2019.

5.7.5 Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome

Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) is an aggressive and life-threatening syndrome characterized by excessive immune activation leading to organ damage. HLH/MAS is typically characterized by high-grade, non-remitting fever, cytopenias, and hepatosplenomegaly, and may be difficult to distinguish from CRS. Laboratory abnormalities found in MAS include elevated inflammatory cytokine levels, serum ferritin, soluble IL-2 receptor (sCD25), triglycerides, and decreased circulating NK cells. Other findings include variable levels of transaminases, signs of acute liver failure, coagulopathy, and disseminated intravascular coagulopathy. HLH/MAS should be considered in the context of refractory or recurrent CRS.

While there are no definitive diagnostic criteria for HLH/MAS, it is typically diagnosed using published criteria for HLH (Schulert 2015).

In the context of CRS after immune effector cell therapy, the following features should raise suspicion of HLH/MAS:

- Absent or poor response of CRS to multiple cytokine-directed therapies and steroids.
- Delayed onset (> 15 days) of the syndrome after immune effector cell therapy.
- Ferritin > 10,000 ng/mL and rapidly increasing; or recurrent increase in ferritin after an initial response to treatment of CRS.
- Abnormal LFT.
- Severe and prolonged pancytopenia.
- Reoccurrence of CRS and/or ICANS after initial response to therapy.

None of these findings are specific for HLH/MAS. However, their presence should prompt evaluation studies and immediate consultation with the Immunotherapy Outpatient Attending or Study Principal Investigator. It is important to assess for other factors such as infection that might mimic or provoke HLH/MAS.

5.7.6 Neutropenia and Thrombocytopenia

Hematological toxicities such as neutropenia, febrile neutropenia, and thrombocytopenia are commonly associated with anticancer agents targeting hematological malignancies such as NHL. Infections and bleeding could occur as the results of severe neutropenia and thrombocytopenia, respectively.

In rat and monkey toxicology studies of NKTR-255, transient mild decreases in platelet and neutrophil counts were observed 72 to 120 hours postdose. Platelet counts increased thereafter and were above baseline levels by 336 hours postdose, indicating recovery. In the monkey, similar transient decreases in neutrophil count were observed 120 hours postdose which recovered by 336 hours postdose.

Patients who experience Grade 3-4 neutropenia should be closely monitored with more frequent assessments as applicable. Use of myeloid growth factor support is allowed. Regular monitoring of platelet count should be performed until the event resolves and dose delays should be considered in cases of severe or life-threatening thrombocytopenia. Transfusion of blood products (eg, platelet transfusion) according to institutional practice is at the discretion of the treating physician.

5.7.7 Infections

Lymphopenia and neutropenia can develop in association with NKTR-255 administration or with the CAR-T cell therapy and can be associated with bacterial or viral infections including reactivation of viral diseases.

Patients with advanced hematologic malignancies may be at an increased risk of infection. Lymphopenia and neutropenia can develop in association with NKTR-255 administration or with the underlying hematological malignancies and can be associated with bacterial or viral infections including reactivation of viral diseases.

Study drug should not be administered in the presence of active infections including hepatitis B, hepatitis C, and HIV. Investigators should exercise caution when considering study drug in patients with history of recurring or chronic infections or with underlying conditions that may predispose patients to infections. Signs and symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment. Prophylactic use of antibiotic, antiviral, or antifungal medication may be considered as clinically indicated and per local standard practice or per National Comprehensive Cancer Network (NCCN) Prevention and Treatment of Cancer-Related Infections Guidelines.

5.7.8 QT/QTc Interval Prolongation

In monkeys, NKTR-255 resulted in transient increases in heart rate, blood pressure, and body temperature, with corresponding transient decreases in PR, QT, and QTc intervals, on the day of dosing compared with vehicle-treated controls. These parameters returned to normal by day 5 postdose, with the exception of the QTc interval. Prolongation of the QTc interval was observed at the high dose of 0.1 mg/kg on days 5, 7, and 14 postdose. Prolonged QTc intervals trended towards, but did not reach, vehicle control values by the end of the study.

Study drug should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least 2 ECG measurements > 30 minutes apart) QTcF that is > 500 ms and > 60 ms longer than the baseline value.
- Sustained absolute QTcF that is > 515 ms.
- An episode of torsades de pointes or a new ECG finding of clinical concern.

If drug-induced arrhythmia including sustained QTcF prolongation is suspected based on ECG changes, consultation with a cardiologist should be obtained and managed as clinically indicated.

In rare circumstances, it may be acceptable to resume study drug, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. The decision to resume study treatment in these circumstances, including the need for dose modification, should be made in conclusion with the Investigator and with Medical Monitor approval.

5.7.9 Tumor Lysis Syndrome

Both lymphodepleting conditioning chemotherapy and CAR-T cell therapy may cause TLS in patients with high disease burden. All patients will be considered at risk for TLS and should receive allopurinol prophylaxis before chemotherapy begins, unless contraindicated. Allopurinol should be continued for as long as the medical team determines appropriate after the infusion. Patients may receive additional hydration and urine alkalinization for the first 2 weeks after infusion. If TLS develops, as defined by the Cairo Bishop criteria (Coiffier 2008), the Attending Physician will direct patient management with guidance from the study staff (Howard 2011). Conservative therapy, including allopurinol, urinary alkalinization, and IV fluid hydration may be instituted immediately for suspected TLS. Hyperkalemia may be treated with potassium-binding resins, diuresis, or insulin/dextrose therapy. Hyperphosphatemia may be treated with phosphate-binding resins. In severe cases, rasburicase (in non-G6PD-deficient individuals) or renal dialysis may be necessary.

5.7.10 Hypogammaglobulinemia and B-Cell Aplasia

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with CAR-T cell therapy. Intravenous immunoglobulin replacement is permitted for clinically significant hypogammaglobulinemia (eg, systemic infection) according to local guidelines. B-cell aplasia is defined as < 3% CD19+CD20+ B cells of lymphocytes by central laboratory review (Mueller 2018).

5.8 Study Assessments

5.8.1 Radiographic Assessments

A standard chest x-ray will be required at screening to rule out any exclusionary disease.

A PET scan and a CT scan (of diagnostic quality) of the neck, chest, abdomen, and pelvis should be obtained approximately 3 and 6 months after CAR-T cell infusion. If a PET/CT is not performed, then the CT scan must be of diagnostic quality. Disease response will be determined according to the Lugano criteria (Appendix 1). The Month 3 scan is to be completed no sooner than 14 days from the most recent dose of NKTR-255 or placebo. A minimum of 28 days is required from the final dose of NKTR-255 or placebo until the month 6 scan. Unscheduled imaging should be performed only with high clinical suspicion, preferably with Medical Monitor consultation.

Patient's disease will further be assessed and at regular intervals as highlighted in the Schedule of Events (Section 1.2) during the post-treatment and long-term follow-up portion of the study. Patients with a response to treatment should have CT of diagnostic quality or PET/CT scans performed at 9 and 12 months (and beyond) after CAR-T cell infusion, as clinically indicated and according to standard of care. The study team may request the results of any imaging restaging. Evaluation of tumor response may be discontinued in patients who proceed to other anti-tumor therapies.

Imaging studies may be omitted in patients who have had recent imaging within 30 days before the scheduled CAR-T cell infusion AND have not received anti-tumor therapy in the interim. Imaging should be performed prior to any lymph node biopsy performed as part of standard of care in patients without palpable adenopathy. For patients with palpable adenopathy, the PET/CT scan may be performed after leukapheresis unless needed to confirm the presence of measurable disease.

Documented tumor measurements are required using PET/CT scans, physical examination, and/or digital photography, as appropriate. The same method of assessment (PET/CT and/or digital photography) and the same technique for acquisition of images must be used for all study assessments (contrast must be used unless medically contraindicated). Baseline imaging should be done at the same institution/facility which will be used to measure response during the patient's participation in the study. Radiographic assessments and efficacy analyses will be conducted by the Investigator site as well as the blinded independent central review (BICR). All treatment decisions will be based on Investigator assessment.

In addition to Investigator's assessment, PET-CT scans of all patients evaluated for disease response will be submitted for BICR. Requirements for PET-CT scans and shipping requirements will be outlined in the study imaging manual.

5.8.2 Tumor Assessments

A unilateral bone marrow aspirate/biopsy should be performed, with pathology and flow cytometry during screening, during the treatment period at Cycle 1 Day 15 (C1D15), and during the follow-up period as clinically indicated. Efficacy assessments will also include measurement of minimal residual disease either by flow cytometry or next-generation sequencing. Polymerase chain reaction (PCR) for IgH clonality and/or fluorescence in situ hybridization (FISH) and other molecular studies may be performed as indicated by the disease. This may be omitted if another bone marrow biopsy was performed within 30 days of planned lymphodepleting chemotherapy **and** the patient has not received anti-tumor therapy in the interim.

Lumbar puncture with cerebrospinal fluid (CSF) evaluation is required for any patient with a history of CNS disease or signs or symptoms of CNS or epidural disease. This may be omitted if a lumbar puncture performed within 30 days of scheduled lymphodepleting chemotherapy did not show evidence of CNS disease.

Bone marrow aspirate and biopsy and lumbar puncture for CSF analysis may be done at C1D15 and at other timepoints as clinically indicated, in patients with lymphoma involvement documented at baseline until the patient achieves a CR. Bone marrow aspirate/biopsy should be performed to confirm CR for patients who have radiographic CR and had known or indeterminant bone marrow involvement at baseline.

Any suspicion of progression should be confirmed with tumor biopsy (if available). Tumor tissue biopsies will be used to characterize infiltrating immune cell populations with immunohistochemistry (IHC) and/or flow cytometry using a panel of markers (including, but not limited to, CD3, CD4, CD8, and CD56).





5.8.6 Electrocardiogram

ECGs will be performed according to the Schedule of Events (Section 1.2).

Patients must be resting quietly in the supine position for ≥ 5 minutes prior to collection of triplicate 12-lead ECG.

The Investigator or qualified Sub Investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant will be reported as an AE as described in Section 7.1. If drug-induced arrhythmia

including sustained QTcF prolongation is suspected based on ECG changes, consultation with a local cardiologist should be obtained and managed as clinically indicated.

5.8.7 Neurological Examination

A neurological examination will be performed with any abnormalities of the following recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, or neuropsychological findings (eg, speech, cognition or emotion). A neurological assessment including Mini-Mental Status Exam should be done according to the Schedule of Events (Section 1.2).

Patient's Immune Effector Cell-Associated Encephalopathy (ICE) score (see Table 13) will also be assessed according to the Schedule of Events (Section 1.2).

5.8.8 Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Events (Section 1.2). Clinical laboratory tests (Appendix 2) will be performed by a designated central laboratory. Central laboratory results must be used to determine patient eligibility. In situations where central laboratory results are unavailable for eligibility determination, the Medical Monitor may approve of substitution of local laboratory results. In these cases, a repeat full set of central laboratory results must be obtained prior to randomization. Clinical laboratory test data will be reviewed by the Investigator or qualified Sub Investigator. Additional clinical laboratory tests may be ordered at the Investigator's or qualified Sub-Investigator's discretion.

For treatment decisions at Cycle 2 and beyond, blood draw for the central laboratory may be obtained up to 5 days prior to the scheduled day of treatment. Depending on the turn-around time for each center, the results of these safety laboratory tests may not be available prior to the scheduled treatment. If the results are not available, or, at the discretion of the Investigator, local laboratory results may be used to determine eligibility for retreatment. In all cases, if local laboratory results are used for retreatment decisions, duplicate central laboratory tests must be submitted to the central laboratory.

Treatment decisions require results for the following tests: hemoglobin, ANC, platelets.

The Investigator or qualified Sub-Investigator will review all laboratory results for clinical significance. Any laboratory result deemed clinically significant (ie, is associated with signs and symptoms, require treatment or require follow-up) will be recorded as an AE as described in Section 7.1.

5.8.9 Physical Examinations

Physical examinations should be conducted according to the Schedule of Events (Section 1.2). Full physical examinations should be conducted at screening/baseline, Day 1 of each cycle, and

EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be reported at screening/baseline, Day 1 of each cycle, and EOT, height at screening/baseline visit only.

5.8.10 Vital Signs

Vital sign measurement will be recorded according to the Schedule of Events (Section 1.2). Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation (PaO_2) (oxygen saturation at screening and on dosing days only), and temperature (oral). Where feasible, vital signs should be measured before having blood drawn for laboratory evaluations.

The study site must be equipped for medical emergencies and have access to an intensive care unit.

If the patient experiences a Grade > 2 IRR or hypotension on the dosing day, the patient may be monitored overnight at the discretion of the Investigator. Longer periods of monitoring may be implemented at the discretion of the Investigator.

5.8.11 Echocardiograms or MUGA Scans

An ECHO or MUGA scan will be performed for all patients during screening or up to 60 days prior to leukapheresis and at EOT to assess cardiac function and LVEF. The same assessment method should be used for the same patient throughout the study.

5.8.12 Pregnancy Tests

Serum or urine pregnancy tests will be performed on women of childbearing potential. Urine pregnancy tests should have a minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin (HCG). A negative pregnancy test result must be obtained before the administration of the study drug(s).

Please refer to Appendix 6 for additional details regarding applicability of pregnancy testing.

If a female patient becomes pregnant, administration of the study drug(s) must be discontinued immediately.

5.8.13 Virology Panel

The serology testing should be as follows:

- Hepatitis C virus (HCV): patients with positive Hepatitis C surface antibody at screening require reflex testing for Hepatitis C RNA.

- Hepatitis B virus (HBV): patients with positive Hepatitis B surface antigen at screening are excluded from the study. Patients with positive Hepatitis B core and negative surface antigen require reflex testing for viral load (Hep B DNA).
- HIV: Patients with HIV-1 or HIV-2 antibody are excluded.

5.9 Blinding

This is a double-blinded study. The Investigator, the patients, and all study site and Nektar personnel involved in study activities, other than those involved in dispensing the study drugs, conducting PK, PD sample analyses, and personnel supporting unblinded monitoring for drug accountability, must remain blinded to each patient's treatment assignment.

In certain rare circumstances when knowledge about the study drug received is required to adequately manage serious adverse reactions or AEs experienced by the patient, and/or for expedited reporting of the serious adverse reactions to the regulatory authorities, it may be necessary to unblind a patient's treatment regimen before all outcome assessments have been performed. If the Investigator believes that the study blind needs to be broken for a patient, a mechanism for unblinding via Interactive Response Technology (IRT) will be available to the Investigator (in addition to designated Sponsor personnel). If the situation permits, the need to break the blind will be agreed by the Investigator and the Sponsor in advance. If the blind is broken, details surrounding the breaking of the blind (eg, date, time, and reason) are to be recorded in the patient's study file.

NKTR-255 will be supplied open label to the clinical site.

An unblinded pharmacist, not involved in any other aspect of the study conduct, will be designated to manage and account for NKTR-255, and to prepare the NKTR-255 or placebo dosing solution for blinded administration to each patient. The pharmacist will ensure that all other study personnel and patients remain blinded to treatment assignment. Study drug accountability for each dose cohort will also be performed by an unblinded monitor not otherwise associated with the day-to-day operational conduct of the study.

The study team will be unblinded at the end of Stage 1 to review the totality of Stage 1 data [redacted]. Details regarding the procedures for maintaining blinding of the study data to ensure study integrity will be described in the unblinding plan.

6.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

6.1 NKTR-255

CCI [redacted]

[redacted]

6.1.2 NKTR-255 Drug Packaging and Labeling

NKTR-255 will be packaged and labeled according to current good manufacturing practices. CCI [redacted] he investigational product will be labeled with the study drug number/name, strength, name of the Sponsor, storage condition, lot number, and the required cautionary statement.

6.1.3 NKTR-255 Drug Reconstitution and Handling

The instructions for reconstitution and administration of NKTR-255 Drug Product are described in the Pharmacy Manual.

6.1.4 NKTR-255 Drug Storage

NKTR-255 Drug Product should be stored in a secure, locked area with temperature at monitored CCI [redacted] as specified on the drug label.

6.1.5 NKTR-255 Drug Shipment

Supply of NKTR-255 Drug Product will be shipped CCI [redacted] to the site pharmacy.

6.2 NKTR-255 Placebo

The placebo dosing solution will be obtained as commercially available 0.9% Sodium Chloride Solution for Injection (USP). Placebo will be identical to NKTR 255 in appearance. An unblinded pharmacist will prepare the placebo for infusion according to the instructions in the Pharmacy Manual.

6.3 Study Drug Accountability and Reconciliation

NKTR-255 will be supplied to the Investigator by Nektar Therapeutics or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

7.0 ASSESSMENT OF SAFETY

7.1 AE Definition and Assessment

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, at any dose, not necessarily related to the treatment.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can also arise from any use of the drug and from any route of administration, formulation, dose, or overdose. This definition includes intercurrent illnesses or injuries, and exacerbation of pre-existing conditions. Clinical laboratory, vital sign, or physical examination abnormalities will only be reported as AEs if they are deemed clinically significant by the Investigator (eg, associated with signs and symptoms, require treatment, or require follow-up). The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

An AE does not include:

- A medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion); an AE is the underlying condition that leads to the procedure.
- Pre-existing diseases or conditions present or detected before start of study drug(s) administration which do not worsen or increase in severity or frequency after the administration of study drug(s).
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery for a condition that has not worsened on study, social and/or convenience admissions to grant families a respite in caring for a patient).
- Overdose of either study drug(s) or concomitant medication without any signs or symptoms.
- Hospitalization for the purpose of facilitating lymphodepleting chemotherapy and/or CAR-T cell infusion is not considered an AE. Any AE requiring prolongation of this hospitalization will be recorded and subject to applicable SAE reporting.

7.2 Monitoring AEs

All AEs will be assessed by the Investigator and recorded including but not limited to, the following: the event term, the date of onset and resolution, seriousness, severity, relationship to study drug(s), outcome, treatment of the event, and action taken with the study drug(s). AEs will be reported starting immediately after the patient has been administered the first dose of study drug (ie, NKTR-255 or placebo) through 30 days after the last dose of study drug or until a new antineoplastic regimen has been initiated, whichever comes earlier.

An event occurring after the patient has provided informed consent, but before the first dose of study drug or confirmed screen failure, will be collected as medical history unless the event is either new AND attributed (related) to protocol-mandated procedures (eg, AEs related to blood draw, lymphodepletion chemotherapy, CAR-T cell therapy, etc.) by the Investigator or there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important AND attributed to the protocol-mandated procedures (eg, AEs related to blood draw, lymphodepletion chemotherapy, CAR-T cell therapy, etc.) by the Investigator. Under the latter 2 circumstances, the event will be considered an AE or SAE and will be captured and reported as such.

Example 1: Thrombophlebitis associated with a blood draw for assessments required prior to dosing per protocol is an event that is related to protocol-mandated procedures. In this scenario, the event of "thrombophlebitis" will be captured as an AE, and it will be documented as being "unrelated" to study drug(s) as applicable.

Example 2: An ankle sprain following an unexpected fall from a flight of stairs while at home, after the patient has provided informed consent, but before the first dose of study drug(s), is clearly unrelated to any protocol-mandated procedures and would therefore be captured as medical history.

7.3 Grading of AEs

The severity of an event and the seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of event is based on the patient/event outcome or action criteria. All AEs will be assessed for severity using the NCI-CTCAE (Version 5.0) guidelines, with the exception of CRS and ICANS, which are graded according to the ASTCT consensus grading as described in Appendix 5. If a particular AE is not listed in the NCI-CTCAE, the following criteria will be used:

- Grade 1 = Mild (event results in mild or transient discomfort, not requiring or needing only minimal intervention or treatment; does not limit or interfere with daily activities [eg, insomnia, mild headache]).
- Grade 2 = Moderate (event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment [eg, fever requiring antipyretic medication]).
- Grade 3 = Severe (event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention).
- Grade 4 = Life threatening or disabling.
- Grade 5 = Death.

AEs will be reported with an individual start and stop date for each level of severity.

7.4 Causality Relationship of AEs

The relationship of each AE to study drug will be evaluated by the Investigator using the following definitions:

- Not related: An AE that does not follow a reasonable temporal sequence from administration of study drug(s), and/or that can be reasonably explained by other factors such as the patient's medical history, preexisting medical condition, underlying disease, concurrent illness, or concomitant medications/therapies.
- Related: There is a reasonable possibility that the AE is caused by the study drug(s). A plausible temporal sequence exists between the time of administration of the study drug(s) and the development of the AE. The AE cannot be reasonably explained by the known characteristics of the patient's clinical state or other concomitant therapies or interventions administered to the patient.

7.5 AE Reporting and Follow-up

All AEs except for SAEs (Section 7.7) will be reported from the time of first study drug administration until 30 days after the last dose of study drug or until a new antineoplastic regimen has been initiated. All ongoing AEs will be followed until resolution, the patient is lost to follow-up, patient death, or until 30 days after last dose of study drug. In case the AE has not completely resolved up to 30 days after the last dose of study drug or until a new antineoplastic regimen has been initiated, the final outcome of these ongoing AEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

For specific instructions on identifying and reporting SAEs, see Sections 7.6 and 7.7.

7.6 Serious AE Definition

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening, that is, in the opinion of the Investigator, the AE places the patient at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization that occurs during the course of a patient's participation in a clinical study, except for those due to the following:
    - A surgery or procedure that was planned before the patient entered the study and which is part of the planned study procedure.
    - Nonmedical reasons, in the absence of an AE.

  - A visit to the emergency room or other hospital department for less than 24 hours that does not result in admission (unless considered an important medical or life-threatening event).
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed above.

Death is an outcome of an AE, and not an AE in itself. All events leading to death, regardless of relationship to study drug, that occur during the protocol-specified reporting period, must be reported with the exception of deaths attributed to disease progression (refer to Section 7.10). An efficacy failure is not considered an SAE. "Life threatening" means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity. "Inpatient hospitalization" means the patient has been admitted to a hospital for medical reasons for any length of time. Additionally, if the patient presents and remains in the Emergency Room for more than 24 hours, the event will have met the inpatient hospitalization criteria. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

7.7 Serious AE Reporting

Serious AEs occurring after the patient has provided informed consent, but before the first dose of study drug or confirmed screen failure, will be collected as medical history, with the exception of the following:

- the event is new AND attributed (related) to protocol-mandated procedures (eg, AEs related to blood draw, lymphodepletion chemotherapy, CAR-T cell therapy, etc.) by the Investigator, or
- there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures (eg, AEs related to blood draw, lymphodepletion chemotherapy, CAR-T cell therapy, etc.) by the Investigator.

In these cases, the events will be reported to Nektar Therapeutics Drug Safety immediately (ie, no more than 24 hours after learning of the event).

In addition, any new or clinically significant changes in the patient's medical and/or cancer history that occur after the first dose of study drug (ie, NKTR-255 or placebo) and meet the SAE criteria will be reported as SAEs. All SAEs regardless of causality attribution or starting

subsequent anticancer therapy, with an onset within **30 days** after the patient's last dose of study drug, will be reported to Nektar Therapeutics Drug Safety immediately (ie, no more than **24 hours** after learning of the event).

In addition, SAEs that are assessed by the Investigator as related to study drug(s) and occurring > 30 days after last dose of study drug, will also be reported to Nektar Therapeutics Drug Safety immediately without undue delay, under no circumstances later than 24 hours following knowledge of the event.

All AEs will be recorded in the electronic case report form (eCRF) database within the timelines outlined in the eCRF completion guidelines. For SAEs, follow the SAE reporting and completion guidelines instructions.

All SAEs will be followed as described in Section 7.8.

Reporting of SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be done in accordance with the standard operating procedures (SOPs) and policies of the IRB/IEC. Adequate documentation must be provided to Nektar Therapeutics, showing that the IRB/IEC was properly notified. Serious AEs will be reported by Nektar Therapeutics or designee to the Regulatory Authorities, per local regulations.

7.8 Serious AE Follow-up

All study treatment-related SAEs that have not resolved within 30 days of last dose of study drug or until a new antineoplastic regimen has been initiated, as applicable, will be followed until any of the following occur (whichever comes first):

- The event resolves.
- The event has stabilized.
- The event returns to baseline, if a baseline value is available.
- It is unlikely that any additional information can be obtained (eg, patient or health care practitioner refuses to provide additional information; lost to follow-up after demonstration of due diligence with follow-up efforts).
- The patient dies or is lost to follow-up.

All ongoing SAEs assessed as "unrelated" to study drug(s) will be followed until resolution or until 30 days after last dose of study drug or until a new antineoplastic regimen has been initiated. In the case where an unrelated SAE has not completely resolved up to 30 days after last dose of study drug or until a new antineoplastic regimen has been initiated, the final outcome of these ongoing SAEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

7.9 Adverse Events of Special Interest

Adverse events of special interest (AESI) will include CRS and ICANS, graded according to ASTCT criteria (Lee 2019).

7.10 Disease Progression – Not Reportable as an AE

It is anticipated that during this study a proportion of patients will experience disease progression prior to study discontinuation. In some patients this may result in hospitalization or death. Such events leading to hospitalization or death of a study patient are typically considered "serious," requiring submission of an SAE report. However, because disease recurrence is an endpoint for this study, reporting the term "disease recurrence" as either an AE or SAE is not necessary.

For all SAEs assessed as clinical manifestations associated with fatal disease progression, the following criteria will apply:

- Seriousness criteria cannot equal Death
- Severity cannot equal Grade 5
- Outcome = Ongoing at time of Death

Deaths that are attributed solely to disease progression by the Investigator should not be reported as SAEs.

However, if there are separate identifiable clinical manifestations of the disease progression that the Investigator is unsure that the events are attributed solely to disease progression (eg, pleural effusion or weight loss), these manifestations are reportable as AEs. Such an event should be recorded on the AE case report form (CRF) and, if the event meets any of the "serious" criteria, it must also be reported on the SAE form.

7.11 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the patients in the study.

7.12 Pregnancy

7.12.1 Pregnancies in Female Patients

The Sponsor must be notified immediately without undue delay, under no circumstances later than 24 hours following knowledge of the initial report and any follow-up reports of a female patient or a male patient's female partner becoming pregnant during the course of the study and for 1 month after the last dose of study drug via the Pregnancy Notification Form. In order for

the Sponsor or designee to collect any pregnancy surveillance information, the pregnant patient or partner must sign an ICF.

Pregnancy, although reportable, is not considered an AE/SAE unless a female patient experiences signs or symptoms of pregnancy complications; however, the contact information for pregnancy reporting is the same as for SAE reporting. Female patients who become pregnant will be followed until the outcome of the pregnancy is known. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring.

If a female patient becomes pregnant, administration of the study drug(s) must be discontinued immediately.

7.12.2 Pregnancies in Female Partners of Male Patients

The Sponsor must be notified within 24 hours of the initial report and any follow-up reports of a female partner of a male patient becoming pregnant during the course of the study and for 1 month after last dose of study drug via the Pregnancy Notification Form. The Sponsor must be notified immediately without undue delay, under no circumstances later than 24 hours following knowledge of the initial report and any follow-up information. All reports should be submitted via the Pregnancy Notification Form. In order for the Sponsor or designee to collect any pregnancy surveillance information, the pregnant patient or partner must sign an informed consent form (see Section 12.2).

Pregnancy, although reportable, is not considered an AE/SAE unless a male patient's female partner experiences signs or symptoms of pregnancy complications; however, the contact information for pregnancy reporting is the same as for SAE reporting. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drugs with the authorization from the pregnant partner. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring.

8.0 ASSESSMENT OF EFFICACY

Disease evaluations will be based on assessments in accordance with the Lugano Classification for NHL treatment response criteria (Appendix 1).

PET/CT using FDG will be utilized to document response or progression to treatment for NHL. PET/CT scans are to be performed per the Schedule of Events (Section 1.2). Bone marrow aspirate/biopsy should be performed to confirm CR for patients who have radiographic CR and had known or indeterminant bone marrow involvement at baseline.

Images will be sent to the central reader. Please refer to the imaging manual for more details.

9.0 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.1 General Considerations

In general, continuous data will be summarized by descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of patients.

A description of analysis methods and detailed definitions for efficacy and safety endpoints will be provided in the statistical analysis plan (SAP).




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9.5 Demographics and Baseline Characteristics

Demographic data (age, sex, ethnicity, body weight) and baseline disease characteristics will be summarized separately for Stage 1 CCI . Details will be included in the SAP.

9.6 Efficacy Analyses

Efficacy analyses will be performed on data provided from BICR (primary analyses) as well as by the Investigator sites for the following efficacy outcomes. Note that the analyses for all efficacy endpoints for Stage 1 CCI will be based on ITT-S1, RE-S1 CCI Populations, respectively.

- **CR rate at month 6 (CRR6):** defined as the proportion of patients who achieve CR at month 6. Patients with CR followed by all-cause death, disease progression, relapse, dropping out, or starting a new lymphoma therapy prior to month 6 are counted as failing to achieve CR at month 6. Patients with CR achieved after starting a new lymphoma therapy prior to or at month 6 are also counted as failing to achieve CR at month 6. The CR rate at month 3 (CRR3) is defined as the proportion of patients who achieve CR at month 3.
- **EFS**: defined as the time from randomization to the earliest date of disease progression per Lugano Classification, commencement of new lymphoma therapy, or death from any cause. Patients who do not have the date of disease progression or date of death will be censored on the date of the last evaluable disease assessment. Patients whose disease progression or death occurs after missing 2 consecutive disease assessments will be censored on the date of the last evaluable disease assessment. Patients who are lost to follow-up will be censored on the date of their last evaluable disease assessment.
- **ORR at month 6 (ORR6):** defined as the proportion of patients who achieve CR or partial response (PR) at month 6. Same algorithm as CR rate at month 6. The ORR at month 3 (ORR3) is defined as the proportion of patients who achieve CR or PR at month 3.
- **Best CRR:** defined as the proportion of patients who have achieved CR as best overall response (BOR). Any CR achieved after starting a new lymphoma therapy will be excluded.
- **Best ORR**: defined as the proportion of patients who have achieved CR or PR as BOR. Same algorithm as best CRR.
- **PFS**: defined as the time from the date of randomization to the date of the first objectively documented progressive disease or death, whichever is earlier. Patients who do not have the date of disease progression or date of death will be censored on the date of the last evaluable disease assessment. Patients who started a new lymphoma therapy prior to disease progression per will be censored on the date of the last evaluable disease assessment prior to receiving the new antineoplastic regimen. Patients whose disease progression or death appears after missing 2 consecutive disease assessments will be censored on the date of the last evaluable disease assessment. Patients who are lost to follow-up will be censored on the date of their last evaluable disease assessment. Please refer to Table 14 for additional details.
- **OS**: defined as the date of randomization to the date of death. Patients who do not have a date of death will be censored on the last date for which the patient was known to be alive.
- **DOR**: defined for patients who have confirmed CR or confirmed PR as the date from first documented CR or PR to the date of the first objectively documented disease progression or death due to any cause, whichever is earlier. Patients who do not have disease progression will be censored on the date of last evaluable disease assessment. Patients who started any new lymphoma therapy, without a prior confirmed progression will be censored at the last evaluable disease assessment prior to initiation of the new lymphoma therapy.

9.6.1 Stage 1

The primary efficacy endpoint is CRR6 per BICR. Secondary efficacy endpoints are CRR3, ORR3, ORR6, best CRR, best ORR, EFS, PFS, and DOR per BICR, and OS. The analyses for the efficacy endpoints will be carried out using both ITT-S1 and RE-S1 Populations.

The number and percentage of patients with CR and objective response (OR) at month 6, best ORR, and best CR rate will be calculated with corresponding 95% confidence interval (CI) using the exact binomial method by treatment groups. Point estimates, p value and 95% CIs for the difference between each NKTR-255 dose group and placebo will be provided.

EFS will be estimated using the Kaplan-Meier method for each arm. The median and its 95% CI, along with the 25% and 75% quartiles will be summarized by treatment groups. EFS rates at months 3, 6, and 12 will be provided.

PFS, OS, and DOR will be analyzed similarly to EFS.




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9.7 Safety Analyses

Safety analyses will be performed CCI [redacted].

AEs and toxicity will be evaluated according to NCI-CTCAE Version 5.0 except for CRS and neurological toxicity that will be evaluated according to ASTCT grading criteria (see Appendix 5). Safety assessments will be performed by medical review of AEs, vital signs, clinical laboratory results, physical examinations, ECGs and cardiac function.

A TEAE is defined as (regardless of intensity):

- Any AE that occurs after study treatment initiation.
- An AE that was present at the time of study treatment initiation but worsened after study treatment initiation.
- An AE that was present and resolved prior to treatment and reappeared after treatment initiation.
- Any treatment-related AE will always be considered treatment-emergent.

TEAEs will be summarized by preferred term, system organ class, cycle, severity grade, and relationship to the study treatment by treatment groups.

All Grade ≥ 3 TEAEs will also be summarized by system organ class and preferred term by treatment groups.

Incidence of AEs of special interest will be summarized separately.

Summary tables for safety analysis by arms and cycles will be provided. Summaries of patients who discontinued study drug(s) due to an AE, AEs leading to death, and AEs leading to dose modifications will be provided.

On study laboratory parameters including hematology, chemistry, liver function, and renal function will be summarized by treatment groups using worst grade as assessed by NCI CTCAE v 5.0. Vital sign abnormalities will be summarized descriptively by treatment groups. A table presenting number and percentage of patients with post-baseline CTC grade increased from baseline (any Grade, Grade 3-4) by treatment group will be provided.

A data listing for deaths will be provided.

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9.9 Data Monitoring Committee

To protect the safety of patients, an independent, external, and multidisciplinary DMC will perform reviews of the efficacy and/or safety data and provide recommendations as to:

1) Whether the data warrant the early termination of the study in the best interests of the patients
2) Whether the study should continue as planned or if the study should continue with modifications, and
3) At the end of Stage 1, CCI

Reviews will be conducted CCI ; details are included in the DMC charter:

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The DMC's specific activities will be detailed in a mutually agreed upon charter, which will define the relevant processes, including meeting proceedings and structure, data assessments, documentation and recordkeeping, process for DMC recommendations, and regulatory reporting, as applicable. The charter will contain procedures to ensure the minimization of bias, such as maintaining confidentiality of any interim data.

10.0 STUDY OR STUDY SITE TERMINATION

The Sponsor has the right to suspend or terminate the study. Sponsor reasons for suspension or termination of the study may include, but are not limited to the following:

- Study is terminated due to safety concerns (ie, the benefit-risk balance is unacceptable).
- Lack of enhanced efficacy signal.
- Development of NKTR-255 is terminated.

If an Investigator suspends or terminates their study site, the Investigator will promptly (if possible, within 24 hours) inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports, summaries, and other documentation as required by health authorities, IRB/IEC, and other regulatory requirements.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

11.1 Changes to the Protocol

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/IEC and the regulatory agency, as required by regulations, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve only logistical or administrative aspects of the study. Any deviation may result in the patient having to be withdrawn from the study and rendering that patient non-evaluable. All protocol deviations and the reasons for such deviations are to be documented and reported to the Sponsor promptly.

11.2 Monitoring

In accordance with Code of Federal Regulations 21 CFR 312.56, International Council for Harmonisation (ICH) GCP, and local regulations, the clinical monitor will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR 312 Subpart D (Responsibilities of Sponsors and Investigators), ICH GCP, and local regulations, the monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs; ensure that all protocol requirements, applicable FDA, ICH GCP, local regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) for the patients in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor. The Investigational New Drug (IND) Application regulations and ICH GCP guidelines also require the Investigator to allow authorized representatives of the Sponsor, IRB/IEC, FDA, and other relevant regulatory authorities direct access to study source records, and to inspect and make copies of the same records. The names and identities of the patients need not be divulged to the Sponsor; however, the records must nevertheless be available to be inspected for review. This can be accomplished by blacking out the patient's name and replacing the name with the patient's study identification number. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the Investigator must inform the Sponsor of these restrictions before initiation of the study.

11.3 Direct Access to Source Data/Documents for Audits and Inspections

The Sponsor or designees may conduct auditing activities of a clinical site at any time during or after completion of the study. The Investigator will be informed of such activities.

Representatives of the FDA or other regulatory agencies, including IRB/IEC representatives, may also conduct an inspection or perform an audit of the study. The Investigator(s)/institution(s) will permit trial-related audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents and study records. If informed of such an inspection, the Investigator shall notify the Sponsor immediately. The Investigator will ensure that the inspectors and auditors have access to the clinical supplies, study site facilities, and laboratory, and that all data (including original source documentation) and all study files are available, if requested.

12.0 ETHICAL CONSIDERATIONS

This study will be conducted to be consistent with the principles that have their origin in Declaration of Helsinki and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with ICH GCP, as well as with any applicable regulatory authority, federal, state and/or local laws and regulations.

12.1 IRB/IEC Approval

Before enrollment of patients into the study, as required by FDA regulations (21 CFR § 56), ICH GCP, applicable regulatory authority requirements, and local regulations, the current protocol, Investigator's Brochure, and ICF will be reviewed and approved by the applicable regulatory authority and/or competent IRB/IEC. A letter documenting the IRB/IEC approval must be received by the Sponsor before the initiation of the study at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol in accordance with Section 11.1.

The Investigator, Sponsor, or their designees will submit a progress report as required by the IRB/IEC. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB/IEC per the IRB/IEC requirements, and in compliance with FDA regulations, applicable regulatory authority requirements, and ICH GCP.

The Investigator, the Sponsor, or their designees shall promptly notify the IRB/IEC of any SAEs, suspected unexpected serious adverse reactions (SUSARs), or any other information that may affect the safe use of the study drug(s) during the study, per the IRB/IEC local requirements, and in compliance with FDA regulations, regulatory authority regulations, and ICH GCP.

12.2 Written Informed Consent

A freely and voluntarily written documentation of informed consent must be obtained from each patient. The content and approval of the ICF must meet requirements of regulations and ICH GCP. Patients will be informed of all aspects of the study that are relevant to the patient's decision to participate, and the ICF must be presented to each patient in the language in which the patient is fluent.

Informed consent will be obtained from and documented for each patient prior to the conduct of any protocol-specific procedures. Signed and dated ICFs will be retained by the Investigator with the study records. Each patient will be given a copy of the signed and dated ICF.

Any pregnancy that occurs in a study patient or the female partner of a male study patient should be reported to the Sponsor or designee. Only if a pregnant patient or partner has signed an informed consent form for disclosure information will the Sponsor or designee be able to collect any pregnancy surveillance information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form (see Section 7.12).

13.0 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection Instruments and Source Documents

13.1.1 Study Records

During the study, the Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports. The Investigator/institution should, at a minimum, maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by the applicable regulatory requirement(s). The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

13.1.2 Data Collection Instruments

Electronic Case Report Forms (eCRFs) will be used in this study. These instruments are used to transmit the information collected during the performance of this study to the Sponsor or Sponsor's designee and regulatory authorities.

The Investigator must review the CRFs for completeness and accuracy and must approve all data, including any changes made. Furthermore, the Investigator retains full responsibility for the appropriateness and accuracy of all data collected in the CRFs.

13.2 Retention of Essential Documents

The Essential Documents contained in the clinical trial master files shall be retained for 25 years or per local and regional regulations and guidelines, whichever is longer. These documents should be retained for a longer period however if required by an agreement with the Sponsor. At all times, the retention must meet applicable data protection laws. It is the responsibility of the Sponsor to inform the Investigator/institution in writing as to when these documents no longer need to be retained.

The Investigator shall archive the clinical trial master file securely and in a way that ensures that it is readily available and accessible, upon request, to the regulatory authorities. Sites must inform the Sponsor in writing if documents will be disposed of per Institutional Policy.

The Investigator will contact the Sponsor before transferring or destroying any study records. The Investigator will also promptly notify the Sponsor in writing in the event of accidental loss or destruction of any study records.

13.3 Confidentiality

Patient confidentiality will be maintained per legal and regulatory requirements and ICH GCP. To comply with GCP guidelines and requirements, patient records will be reviewed during monitoring visits and audits conducted by the Sponsor, Sponsor's representatives, or health authorities. During these activities, every reasonable effort will be made to keep medical information, including patient identifying information, as confidential as possible as required by law.

Study data given to, and used by, Nektar are protected by the use of a patient identification number. The assignment of unique patient identification number to each patient by IRT system enables de-identification.

Demographic identifiers that will be collected as part of Study Data include year of birth, age, gender, race, and ethnicity provided this is permitted under applicable laws. Exact date of birth and patient name/initials are not collected.

The study site is not to attach the names or other directly identifying information of the patients to any Study Data or biological samples that will be transferred to Nektar. Only pseudonymised/ key-coded Study Data and biological samples will be transferred to Nektar, and only the study site will be able to connect the patient identification number to a patient’s personal data.

13.4 Security Measures

Sites will employ both technical and organizational measures (such as, but not limited to, controlling access to personal patient data to only those with a need to know such data, data encryption, data anonymization and pseudonymization, and so forth) to ensure patient and patient data privacy. Sites will adhere to a “privacy by design” and “privacy by default” approach in collecting, storing, and processing personal patient data.

In the event of a breach of the security measures used by the Site to ensure patient and patient data privacy, the Site will immediately notify the Sponsor.

14.0 PUBLICATION POLICY

All data are the property of the Sponsor. Any formal presentation or publication of data from this study will be considered for joint publication by the Sponsor personnel and Investigator(s).

Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement governing participation in the study. Study data shared by Nektar will not contain patient identifiable information.

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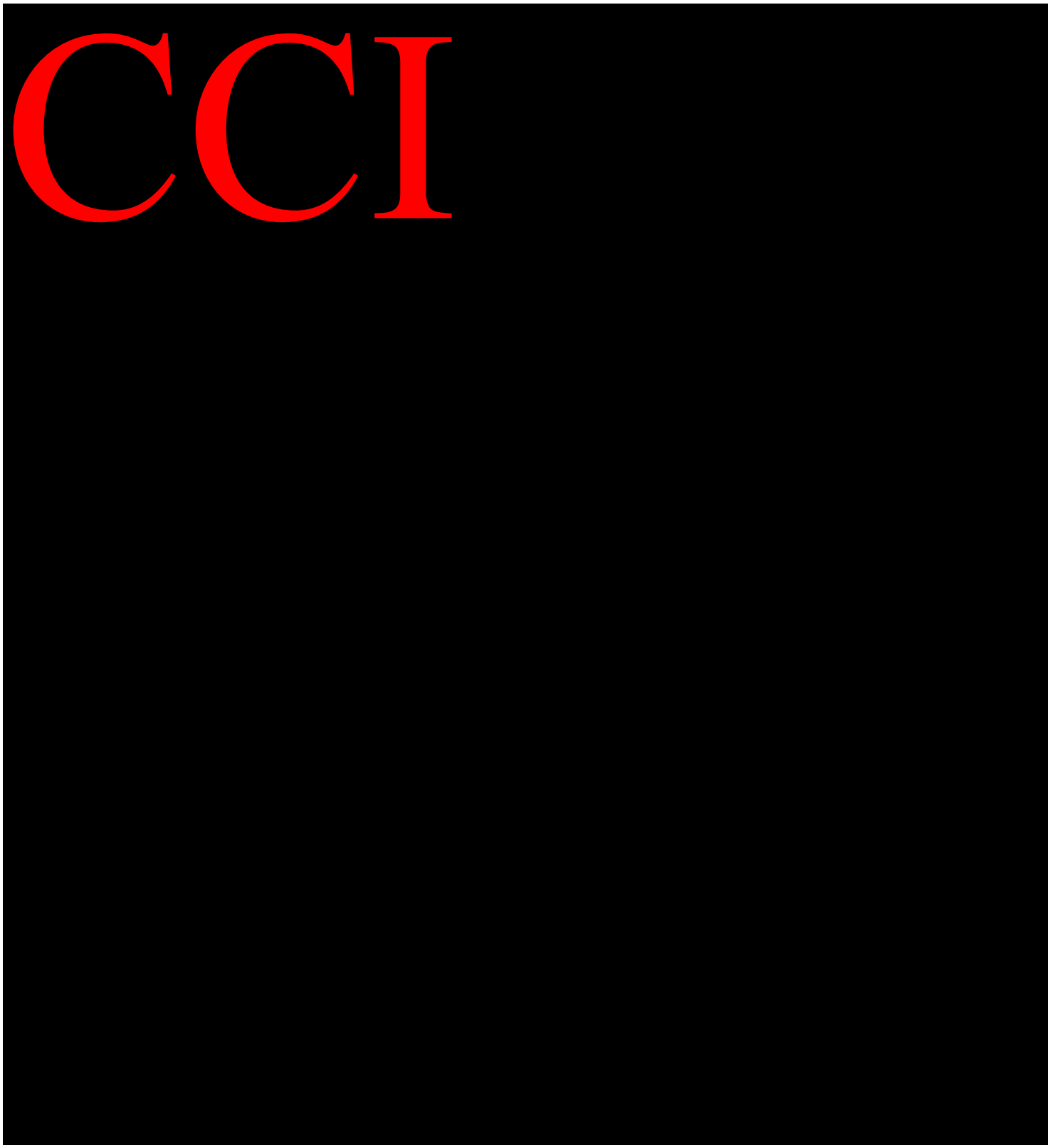

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