Statistical Analysis Plan Version 1.0 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: 29 April 2024

Nektar Therapeutics

Statistical Analysis Plan

A PHASE 2/3, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTI-CENTER 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, Amendment 1.0
SAP Version:	1.0
Date:	April 29, 2024


PPD

TABLE OF CONTENTS

TABLE OF CONTENTS **3**
LIST OF ABBREVIATIONS **5**
1.0 ADMINISTRATIVE STRUCTURE **8**
2.0 INTRODUCTION **9**
3.0 STUDY OBJECTIVES **10**
3.1 Primary Objectives 10
3.2 Secondary Objectives 10
CCI [redacted]
4.0 STUDY ENDPOINTS **12**
4.1 Primary Endpoints 12
4.2 Secondary Endpoints 12
CCI [redacted]
5.0 OVERALL STUDY DESIGN AND PLAN **14**
6.0 STATISTICAL CONSIDERATIONS **16**
6.1 General Considerations 16
CCI [redacted]
CCI [redacted]
6.4 Handling of Missing Data 18
6.5 Conversion between Day, Month and Year 20
6.6 Definitions 21
6.6.1 Definitions Related to Endpoints 22
7.0 STATISTICAL ANALYSIS **26**
7.1 Patient Disposition 26
7.2 Protocol Deviations 26
7.3 Study Population 27
7.3.1 Demographics and Other Baseline Disease Characteristics 27
7.3.2 Randomization and Stratification Factors 27
7.3.3 Cancer History and Prior Cancer Treatment 28
7.3.4 Medical and Surgical History (Non-Cancer Related) 29
7.3.5 Prior Transplant and Prior Radiotherapy 29
7.3.6 Neurological Exam and Lumbar Puncture 29
7.4 Treatments and Medications 29

7.4.1 Prior and Concomitant Medications....29
7.4.2 Study Drug Exposure and Modification....30
7.5 Efficacy Analysis....30
7.5.1 Objective Response Rate, and Complete Response Rate....31
7.5.2 Duration of Response and Time to Response....31
7.5.3 Progression Free Survival (PFS)....31
7.5.4 Overall Survival....31
7.5.5 Event Free Survival....32
7.6 Safety Analyses....32
7.6.1 Adverse Events....32
7.6.2 Death....34
7.6.3 Clinical Laboratory Evaluation....34
CCI [redacted]
8.0 DATA MONITORING COMMITTEE AND SAFETY REVIEW COMMITTEE....38
[redacted]
10.0 CHANGES TO PROTOCOL-SPECIFIED ANALYSES....48
11.0 REFERENCES....49

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
CCI	
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute Neutrophil Count
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BICR	Blinded Independent Central Review
BLRM	Bayesian Logistic Regression Model
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BOR	Best Overall Response Rate
C1D1	Cycle 1 Day 1
calCrCL	Calculated Creatinine Clearance
CAR-T	Chimeric Antigen Receptor T (cell)
CCI	
CI	Confidence Interval
CRR	Complete Response Rate
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee

DOR	Duration of Response
DSMC	Data Safety Monitoring Committee
DSS	Data Science and Systems
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EFS	Event Free Survival
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration
CCI	
GGT	Gamma-glutamyl Transferase
IRT	Interactive Response Technology
CCI	
KM	Kaplan Meier
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
CCI	
MR	Minimal Response
MRD	Minimal Residual Disease
MTD	Maximum Tolerated dose
NA	Not Analyzed
NHL	Non-Hodgkin Lymphoma
CCI	
NR	Not Received
ORR	Objective Response Rate

OS	Overall Survival
PD	Progressive disease
PFS	Progression-free Survival
PI	Principal Investigator
CCI	
PR	Partial Response
PT	Preferred Term
CCI	
CCI	
SAE	Serious Adverse Event
CCI	
SOC	System Organ Class
SRC	Safety Review Committee
CCI	
CCI	
TB	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TTR	Time to Response
CCI	
ULN	Upper Limit of Normal
WHODrug	World Health Organization's Drug
WBC	white blood cell

1.0 ADMINISTRATIVE STRUCTURE

This study will be managed via a partnership between Nektar Therapeutics and a contract research organization (CRO). Central clinical laboratories will be used for processing CCI [redacted] samples. An interactive response technology (IRT) service provider will manage patient enrollment, study drug(s) distribution and inventory management. Data for this trial will be entered into an Electronic Data Capture (EDC) system, using a CCI [redacted] platform. An independent data monitoring committee (DMC) has been established to review the safety data on a periodic basis. Response and progression will be determined based on Lugano assessment for non-Hodgkin's lymphoma patients.

2.0 INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Nektar Therapeutics 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 or refractory large B-cell lymphoma", protocol amendment 1.0 dated 08 October 2022. The purpose of this plan is to describe the statistical analyses according to Section 9 of the study protocol and along with any additional analyses, specifications or deviations from the protocol planned. Any deviations from these guidelines will be documented in the clinical study report (CSR). The efficacy and safety data by treatment arm during study will be conducted separately for each stage. The study stops enrollment at Stage 1 with 15 patients, hence this plan will focus on Stage 1 (including NKTR-255 or placebo following CAR-T cell therapy).

CCI [redacted]

3.0 STUDY OBJECTIVES

This section shows planned primary, secondary, CCI objectives from the study protocol amendment 1.0 dated 08 October 2022. This plan will focus on addressing the Stage 1 (NKTR-255 followed by CAR-T cell therapy: axicabtagene ciloleucel or lisocabtagene maraleucal) related objectives only. Due to early study termination, Blinded Independent Central Review (BICR) data is not complete. Hence the analyses for the primary endpoint of 6-month Complete Response Rate (CRR) by BICR, and the analyses for the secondary endpoints of 3-month CRR, best CRR, 3 and 6-month Overall Response Rate (ORR), best ORR, Duration of Response (DOR) and Progression Free Survival (PFS) by BICR will ONLY be performed based on Principal Investigator (PI) data in the final study CSR.

3.1 Primary Objectives

Stage 1:

- To compare the CRR by BICR at month 6 of treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.

3.2 Secondary Objectives

Stage 1:

- 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 CRR 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 and OS following treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.


CCI

4.0 STUDY ENDPOINTS

This section shows planned primary, secondary, CCI endpoints which are related to Stage 1 (NKTR-255 or placebo following CD19-directed CAR-T cell therapy: axicabtagene ciloleucel or lisocabtagene maraleucal). Due to early study termination, Blinded Independent Central Review (BICR) data is not complete. Hence the analyses for the primary endpoint of 6-month Complete Response Rate (CRR) by BICR, and the analyses for the secondary endpoints of 3-month CRR, best CRR, 3 and 6-month Overall Response Rate (ORR), best ORR, Duration of Response (DOR) and Progression Free Survival (PFS) by BICR will ONLY be performed based on Principal Investigator (PI) data in the final study CSR.

4.1 Primary Endpoints

- Compare Complete response rate (CRR) by BICR at month 6 of treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.

4.2 Secondary Endpoints

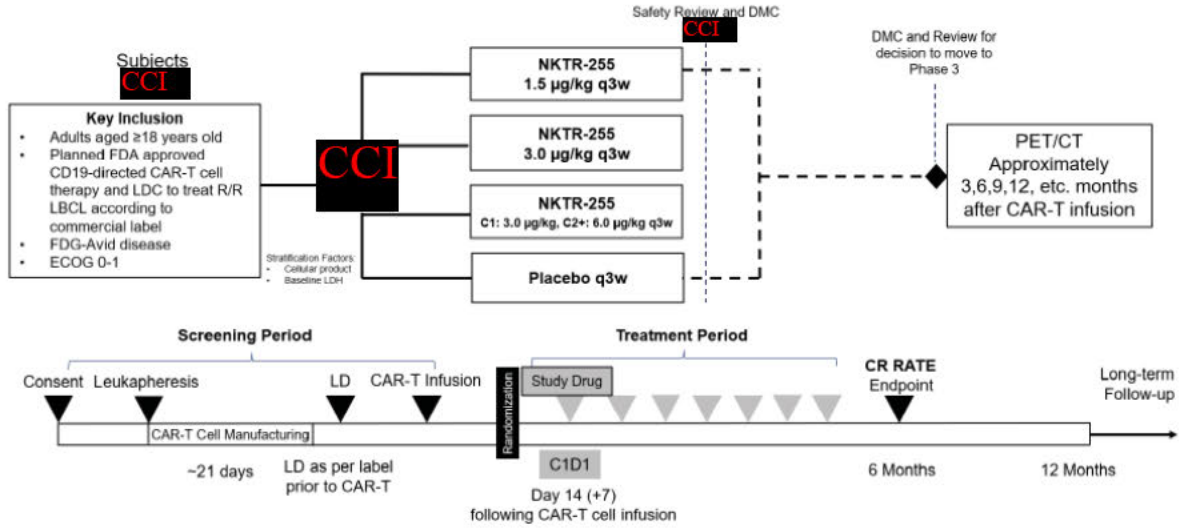
- Incidence of TEAEs in Stage 1 following treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.
- Clinical laboratory tests, Vital Signs, ECG, physical examination, ECHO/MUGA
- Complete response rate (CRR) by BICR at month 3, Overall response rate (ORR) by BICR at month 3 and 6, best CRR, and best ORR based on Lugano classification following treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.
- Duration of response (DOR) and Progression Free Survival (PFS) by BICR, Event Free Survival (EFS), and Overall Survival (OS) following treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy.


CCI

5.0 OVERALL STUDY DESIGN AND PLAN

This study is a Phase 2/3, randomized, double blind, placebo-controlled, multicenter dose study of NKTR-255 vs Placebo following CD19-Directed CAR-T Cell therapy in patients with relapsed/refractory large B-Cell lymphoma. Figure 1 shows the Stage 1 planned study design protocol amendment 1.0 dated 08 October 2022.

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.

Figure 1: Study Design

The design described here will focus on Stage 1. Approximately CCI patients will be enrolled, and patients will R/R LBCL who have been treated with CAR-T cell therapy will be randomized CCI [redacted] to receive either 1.5ug/kg, 3.0ug/kg, 3.0/6.0ug/kg of NKTR-255, or placebo. Among the treatments, 3.0/6.0ug/kg NKTR-255 is a step-up dose regimen initiating with 3.0ug/kg NKTR-255 in Cycle 1 (C1) and continuing in Cycle 2 and subsequent cycles (C2+) with 6.0ug/kg NKTR-255.

Randomization will be stratified according to:

- The cellular product that the patient receives (ie, axi-cel or liso-cel)
- 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.

Patients must meet additional requirements for study drug administration 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 dosing criteria (ie, maximum period between CAR-T cell therapy and study drug infusion on Cycle 1 Day 1 [C1D1] is 21 days)
- For Cycle 2 and beyond, a dose may be delayed for a maximum of 21 days until a patient meets dosing criteria

At the end of Stage 1, the DMC will review safety CCI data from all available arms to make go/no-go and dose selection recommendations CCI.

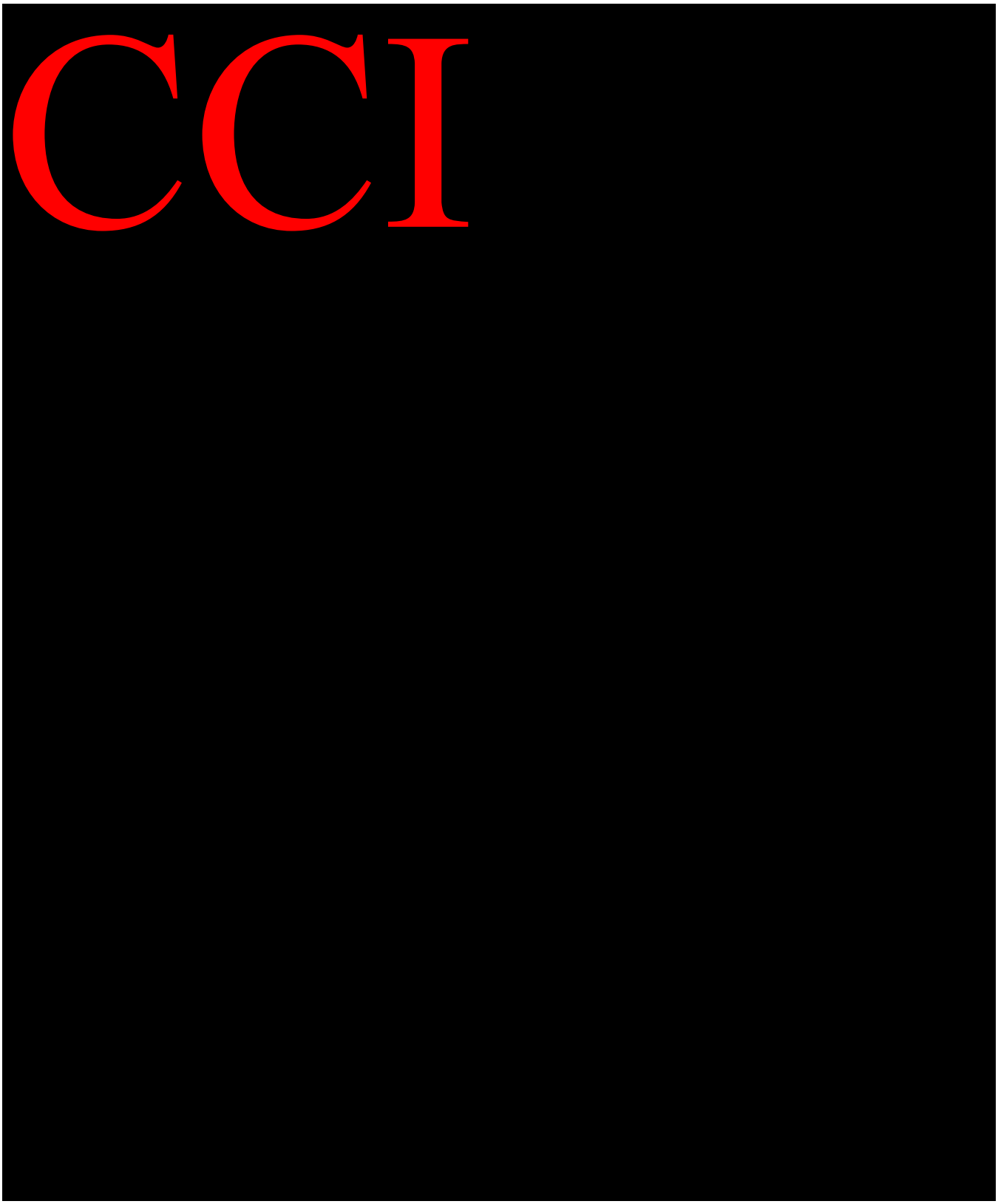
6.0 STATISTICAL CONSIDERATIONS

6.1 General Considerations

The statistical analyses will be reported using summary tables, data listings and graphics as appropriate.

Unless otherwise specified, data collected from patients will be presented by dose level group, placebo and overall.



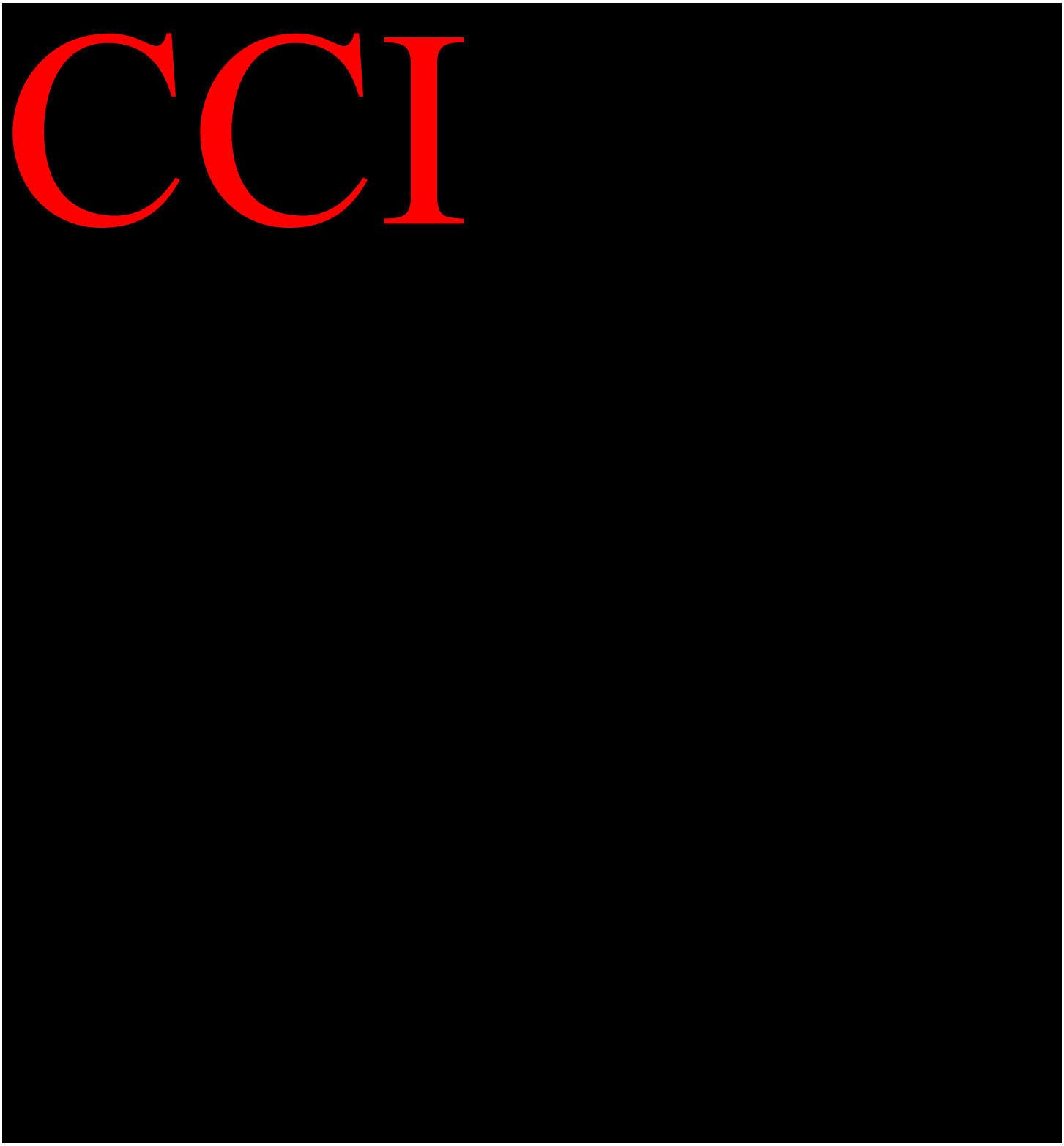

CCI

CCI

6.4 Handling of Missing Data

Every effort will be made to avoid missing/partial on-study data.

CCI


CCI



6.5 Conversion between Day, Month and Year

Conversions between different time unit will be based on days. For conversion to month and year, the following formula are used: month=days/30.4375, year=days/365.25.

Days of duration and time to events are calculated with the following formula:

(later assessment or study treatment [or follow-up] end date) – (earlier assessment or study treatment start date) +1.

6.6 Definitions

Study drug or study treatment: For patients in Stage 1, study drug or study treatment refers to treatment with NKTR-255 vs placebo in patients who have received CD19-directed CAR-T cell therapy (axicabtagene ciloleucel or lisocabtagene maraleucel).

Baseline: Unless otherwise specified, the baseline value for each variable is the last non-missing value collected at the time (if collected) closest to, but prior to, the start of NKTR-255 administration. For triplicate ECG data, the record with three non-missing value will be considered as non-missing. If multiple measurements occur on the same day at the same time, or on the same day but the time is not available, the average of the measurements (for continuous data) will be considered the baseline value. When dosing times and/or observation times are not collected, it is assumed that protocol planned in-office assessments obtained on the day of the first dose of study drug are prior to administration of the first dose of study drug and therefore considered baseline values.

Study day: Study Day 1 (C1D1) is defined as the day of first infusion of any study drug (NKTR-255 or Placebo). Study Day -1 is defined as the day before first infusion of study drug.

Last known alive date: If the death date for a patient is known, then the last known alive date will be the death date. Otherwise, it will be derived as the latest one captured from the multiple sources listed as below:

- The latest date of patient assessment for blood draws CCI [redacted], vital signs, ECG, tumor assessments, ECOG, or tumor biopsy dates
- The latest date of subsequent anti-cancer therapies
- AE start or end date
- Concomitant medication start or end date
- Date of the last survival follow-up visit if the patient's status is 'alive'
- Study treatment start or end date
- Discontinuation date if the reason for the patient's discontinuation is not "lost to follow-up"



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.

6.6.1 Definitions Related to Endpoints

Absolute value (and/or percent) change from baseline: Absolute value change and or percent change from baseline will only be summarized for patients with both baseline and post-baseline values for the relevant visit and will be calculated as:

Change from baseline = post-baseline value – baseline value

Percent change from baseline = (post-baseline value – baseline value)/baseline value*100

Treatment-emergent adverse events (TEAE):

- 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.

Treatment-emergent adverse events (TEAE) period: Start of NKTR-255 through 30 days post last dose NKTR-255, or until a new antineoplastic regimen has been initiated, whichever comes first.

Prior medications: Prior medications are defined as medications with a start date prior to C1D1 (the first infusion date of any study drug), regardless of when the stop date is.

Concomitant medications: Concomitant medications are defined as all prescription medications with stop date after C1D1, or medications with start date on or after C1D1 and up to 30 days after the last dose of NKTR-255, if applicable. CCI [redacted]

Medications with start date prior to C1D1 and end date after C1D1 will be classified as both prior and concomitant medications.

Permitted Medication: Premedication with antihistamine with acetaminophen must be administered approximately 30 to 60 mins prior to each infusion of NKTR-255/placebo.

Best overall response (BOR): The BOR is defined as the best response designation over post-baseline response assessments in the following order: CR, PR, SD, PD, NE for NHL patients. Disease assessments beyond progression or after start of subsequent therapy will not be considered for BOR.

Complete response rate at month 6 (CRR6): The CRR at month 6 is defined as the proportion of patients who have achieved 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.

Best Complete response rate (CRR): The CRR is 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.

Objective response rate at month 6 (ORR6): The ORR at month 6 is defined as the proportion of patients who have achieved CR or PR at month 6. Same algorithm as CR rate at month 6. The ORR at month 3 (ORR3) is defined as proportion of patients who achieved CR or PR at month 3.

Best Objective Response Rate (ORR): The ORR is defined as proportion of patients who have achieved CR or PR as BOR. Same algorithm as best CRR.

EFS: The EFS is 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. CCI [redacted]

Responders: Responders are defined as patients who at least achieved partial response (PR).

Duration of response (DOR): DOR is defined as 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. This endpoint is only applied for responders.

Time to Response (TTR): Time to response is defined as the time from randomization date to

first response (PR or better). This endpoint is only applied for responders.

Time to Complete Response (TTCR): Time to complete response is defined as the time from randomization date to first complete response. This endpoint is only applied for responders.

Progression free survival (PFS): Progression-free survival is 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 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 the date of progression disease or death due to any cause, whichever occurs first. The censored following the rules specified below.



[redacted]

Overall Survival (OS): OS is defined as the date of randomization to the date of death. Patients who do not have date of death at data cut-off date will be censored at their last date known to be alive. Patients who do not have any follow-up since randomization date will be censored on the first dose date.

7.0 STATISTICAL ANALYSIS

7.1 Patient Disposition

The summary for patient disposition includes the number and percentage of patients for the following categories: patients discontinued from each study treatment and reasons for treatment discontinuation, patients discontinued from the study and reasons for study discontinuation.

[redacted]

7.2 Protocol Deviations

Protocol deviations will be classified as significant or non-significant and grouped into categories. A protocol deviation that affects primary efficacy and safety assessments (as applicable), the safety or mental integrity of a subject, or the scientific value of the trial is considered as significant protocol deviation.

The number and percentage of patients with significant protocol deviations in each category will be summarized. Significant protocol deviations will be provided in listings.

7.3 Study Population

7.3.1 Demographics and Other Baseline Disease Characteristics

Demographic and baseline characteristics will be summarized for the Stage 1 ITT Population.

Demographic variables include the following:

- Age at enrollment
- Age categorization (< 65, ≥ 65 years)
- Sex
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, and unknown)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported, and Unknown)

Baseline characteristics include:

- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- ECOG status
- Childbearing Potential (Female)

No inferential statistics will be generated. Demographic and baseline characteristics data will also be presented in a by-patient listing.

7.3.2 Randomization and Stratification Factors

Stratification factors and the subgroup interaction will be listed for the Stage 1 ITT Population.

Stratification factors are listed as the following:

- The cellular product that the patient receives (ie, axi-cel or liso-cel [Stage 1]
- Baseline LDH (defined as LDH ≥ 440 U/L or < 440 U/L prior to lymphodepletion confirmed by central laboratory)

The randomizations for Stage 1 will take place no more than 1 day prior to the first study drug administration.

7.3.3 Cancer History and Prior Cancer Treatment

The NHL cancer history will be summarized as following for the Stage 1 ITT (ITT-S1) populations:

NHL cancer history
• Disease subtype (Diffuse Large B-Cell Lymphoma, High Grade B-Cell Lymphoma, Primary Mediastinal Largest B-Cell Lymphoma, Follicular Lymphoma, Other) • Transformation Prior diagnosis (Follicular Lymphoma, Richer Transformation, Other) • Time from initial diagnosis to randomization • Molecular Classification (Germinal center B cell like, Non-Germinal center B cell like) • Non-Germinal Center B-cell like subtype (Activated B cell like, Type 3) • Lugano classification (I, II, III, IV) • Secondary Age-Adjusted IPI Score (low 0-1, low-intermediate 2, high-intermediate 3, high 4-5) • Bulky disease, one node>7cm (Y/N) • Bone marrow involvement (Y/N) • Extranodal involvement (Y/N) • CNS or epidural disease (Y/N) • Chromosomal Abbreviation (Y/N, if Y, MYC, BCL6, BCL2, Other) • Chromosomal Abbreviation Evaluation Method (FISH, Other)

The most recent line of prior cancer treatment will be summarized, and all prior cancer therapy will be listed.

7.3.4 Medical and Surgical History (Non-Cancer Related)

All medical and non-cancer related surgical history will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT). Patients will be counted only once within each SOC and PT.

7.3.5 Prior Transplant and Prior Radiotherapy

Prior transplant and radiotherapy will only be provided in a listing.

7.3.6 Neurological Exam and Lumbar Puncture

Neurological Exam and Lumbar Puncture will only be provided in a listing.

7.4 Treatments and Medications

7.4.1 Prior and Concomitant Medications

All medications will be coded by the WHO Drug using ATC level 2 term and PT. The number and percentage of patients who have received each prior medication and who have received each concomitant medication will be summarized by ATC level 2 term and PT. Patients will be counted only once under each ATC level 2 term and preferred term. Prior or concomitant medications are defined in Section 6.6.1 and will be classified based on recorded or imputed start dates of medication taking with rules specified in Section 6.4.

Concomitant medications will be summarized, all prior and concomitant medications will be listed.

7.4.2 Study Drug Exposure and Modification

Study drug exposure and NKTR-255 dose modification will be summarized and listed for the Stage 1 safety CCI population and breakdown by treatment arm. For each patient, the NKTR-255 dose will be calculated based on the patient's weight in kilograms collected at each dose administration, and dose intensity will only be included in the listing. If weight is missing for the visit, the most recent weight collected will be used.



7.5 Efficacy Analysis

Disease assessments at both scheduled and unscheduled visits will be used for efficacy endpoints. Disease assessments after new systemic anti-cancer therapy, surgical procedures or radiotherapy on target lesions will be excluded. Treatment beyond progression is allowed for qualified patients. However, tumor assessment beyond progression will not be considered for response endpoints.



7.5.1 Objective Response Rate, and Complete Response Rate

BOR (CR, PR, SD, PD, NE) will be summarized by Lugano Classification. Number and percentage of patients who achieved CR or PR (ORR) and who achieved CR (CRR) will the summarized with 95% CIs. CRR6, CRR3, ORR3, ORR6, best CRR and best ORR will be summarized.

7.5.2 Duration of Response and Time to Response

The DOR will be summarized for responders as determined by PI. Median and 95% CI for DOR among responders will be estimated. The quartiles (25%, median, and 75%) of DOR and 95% CI for median DOR will be provided by Kaplan-Meier method. Along with DOR statistics, the number and percentage of patients who have events or censored will also be presented. Among the responders, patients who remain alive and have not progressed are continued responders and are censored on the last evaluable disease assessment date (prior to subsequent cancer therapy). The number and percentage of continued responders will be presented. Summary statistics of TTR and TTCR will also be provided for responders. A listing instead of summary tables may be provided for DOR and TTR and TTCR if there are not sufficiently large number of confirmed responders.

7.5.3 Progression Free Survival (PFS)

Investigator assessed PFS will be summarized descriptively using the Kaplan-Meier (KM) product-limit method. KM estimate of PFS rates at 3, 6, 12 months will be calculated. Quartiles (25%, median and 95% confidence interval, and 75%) of PFS, along with two-sided 95% CIs (based on the log-log transformation) for median PFS will be calculated. The reasons of PFS events (death vs. progression) will be summarized. PFS KM curve will be plotted.

7.5.4 Overall Survival

OS will be summarized descriptively using the Kaplan-Meier (KM) product-limit method. KM estimate of OS rates at 3, 6 and 12 months will be calculated. Quartiles (25%, median and 95%

confidence interval, and 75%) of OS, along with two-sided 95% CIs (based on the log-log transformation) of median OS, will be calculated. OS KM curve will be plotted.

7.5.5 Event Free Survival

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.

7.6 Safety Analyses

Unless otherwise specified, all safety analyses will be based on the Stage 1 safety (Safety-S1) population. All summaries will be provided by dose groups and treatment regimens.

7.6.1 Adverse Events

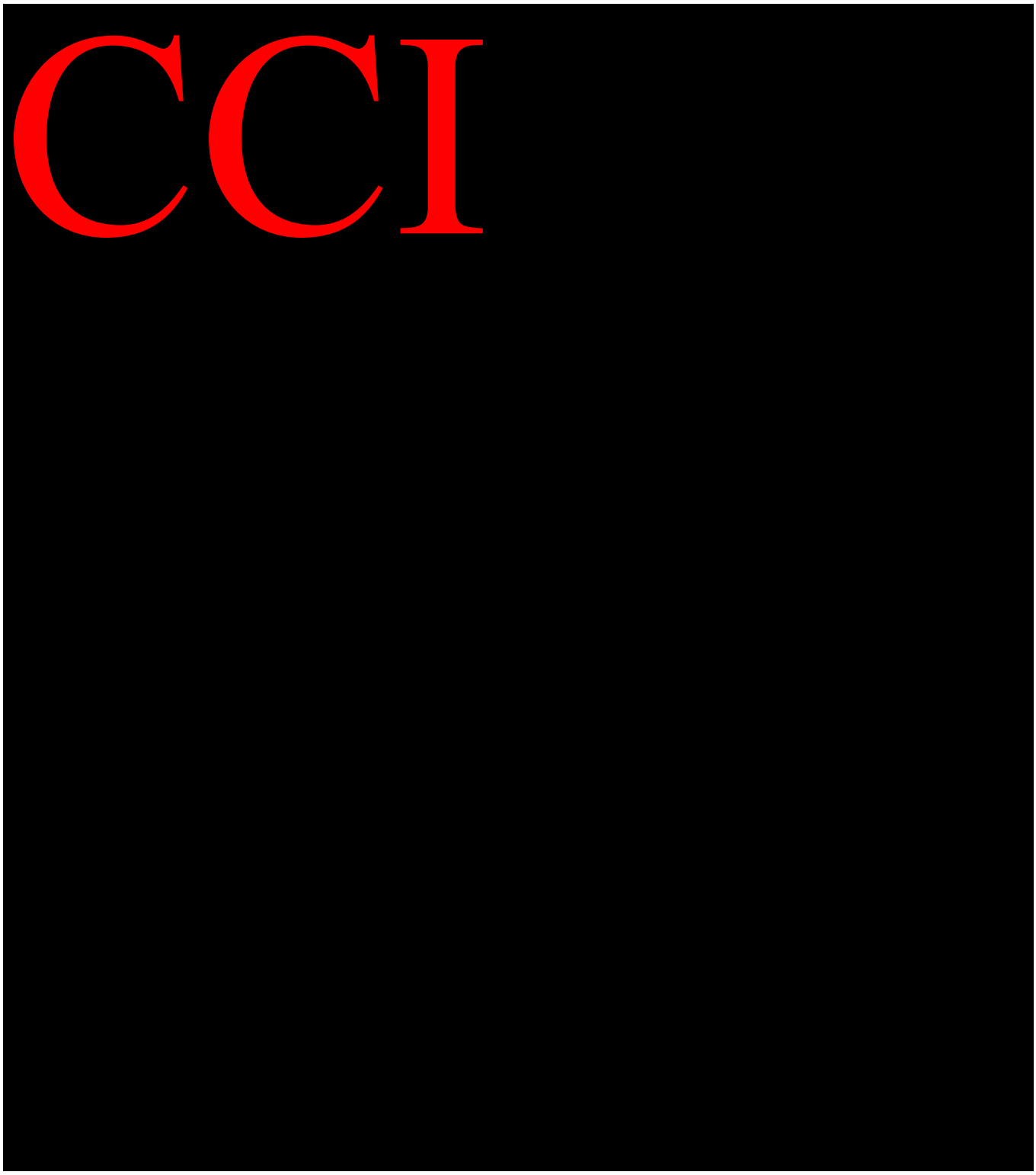
All AEs will be included in separate listings: AE between CAR-T and first dose of NKTR-255, AE after first dose of NKTR-255. TEAE period defined in Section 6.6.1 will be applied for TEAEs summaries. Verbatim terms on case report forms will be mapped to PTs and SOCs using the Medical Dictionary for Regulatory Activities (MedDRA) (version 25.1). CRS events are graded based upon American Society for Transplantation and Cellular Therapy (ASTCT) criteria. All other AEs are graded based upon CTCAE version 5.0.

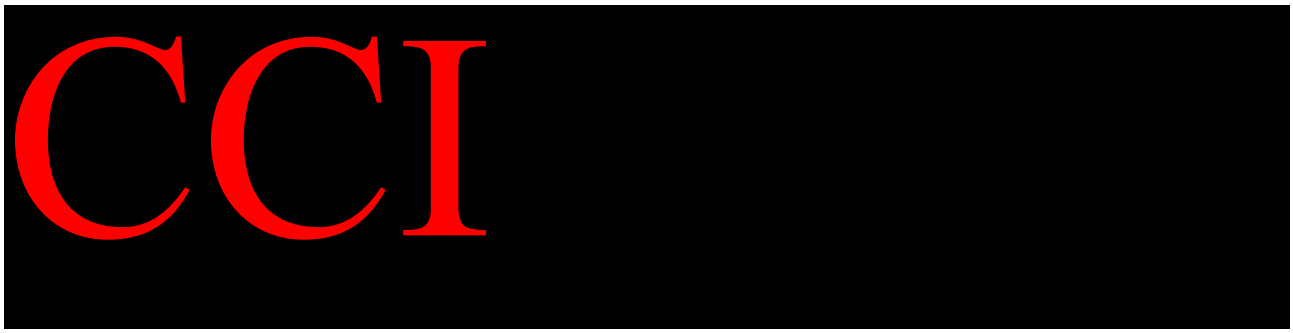
TEAEs will be summarized by PT, SOC, CTCAE grade of severity, and relationship to the study treatment. For patient level summaries, patients with multiple occurrences of events of the same PT and SOC will be counted once. By worst CTCAE grade tables will include 4 categories, which are Grade 1-2, Grade 3, Grade 4, and Grade 5.

The following AE summaries will be provided in Stage 1 safety CCI [redacted] population

- Overall summary of TEAEs
- TEAEs by SOC and PT

- Grade 3 and above TEAEs by SOC and PT





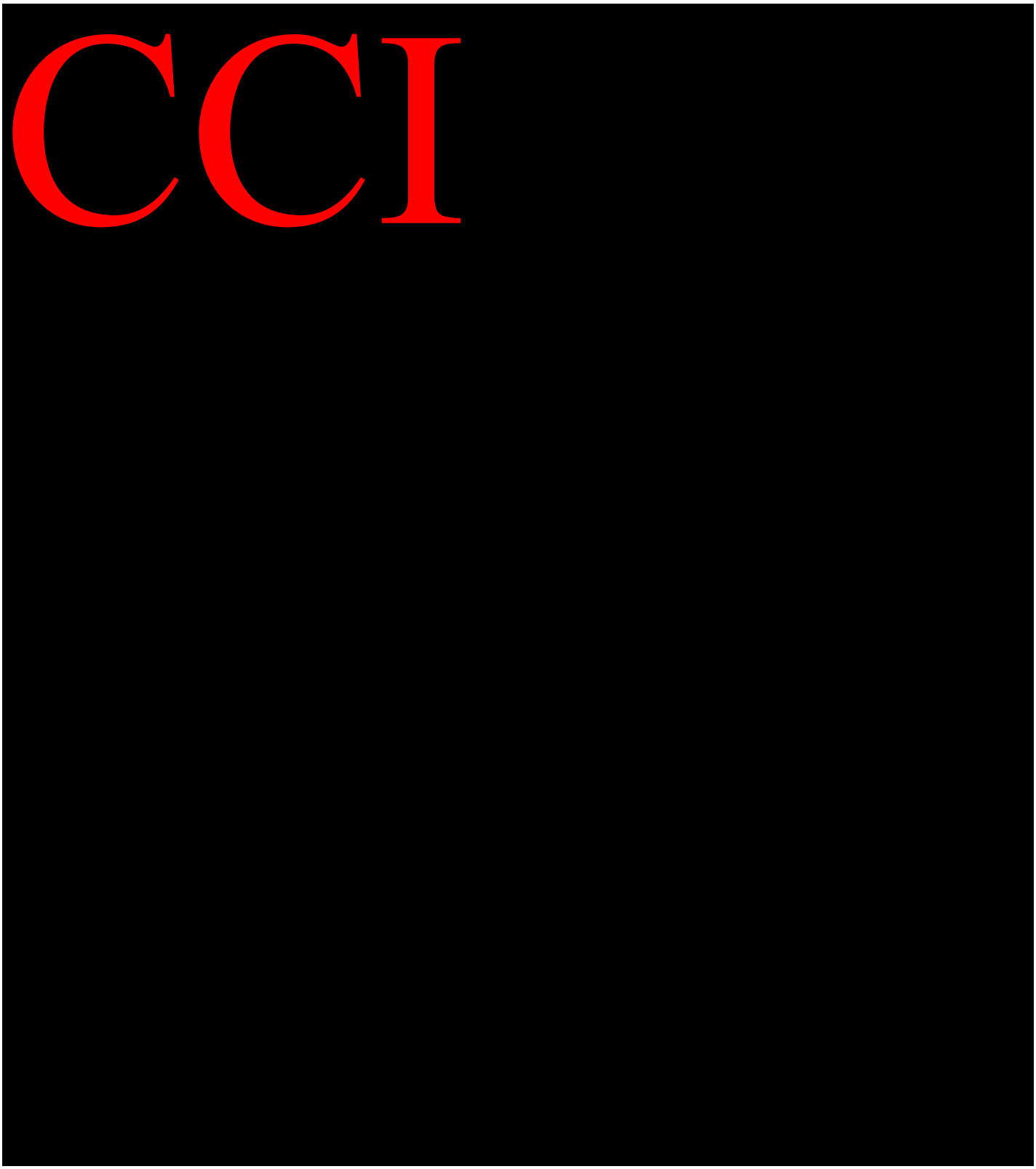
7.6.2 Death

A by-patient listing of on treatment and follow up deaths (If there are no follow up death, this listing will not be provided) for all Stage 1 CCI patients.

7.6.3 Clinical Laboratory Evaluation

Clinical laboratory tests will be conducted according to the Schedule of Assessments and performed by the designated central laboratories. Analyses of laboratory parameters include values collected until 30 days, but before the initiation of subsequent anticancer treatment.




CCI


CCI

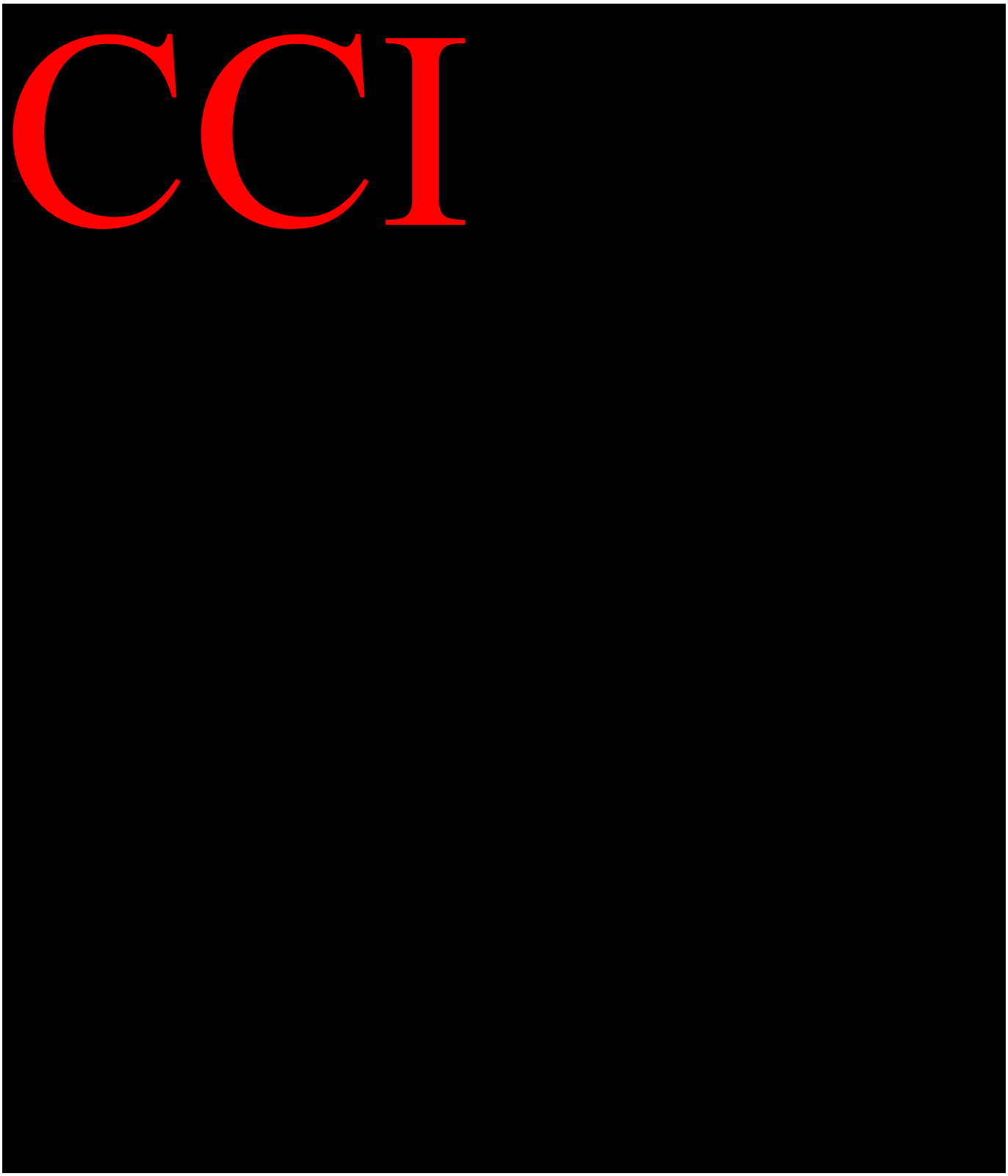

CCI

8.0 DATA MONITORING COMMITTEE AND SAFETY REVIEW COMMITTEE

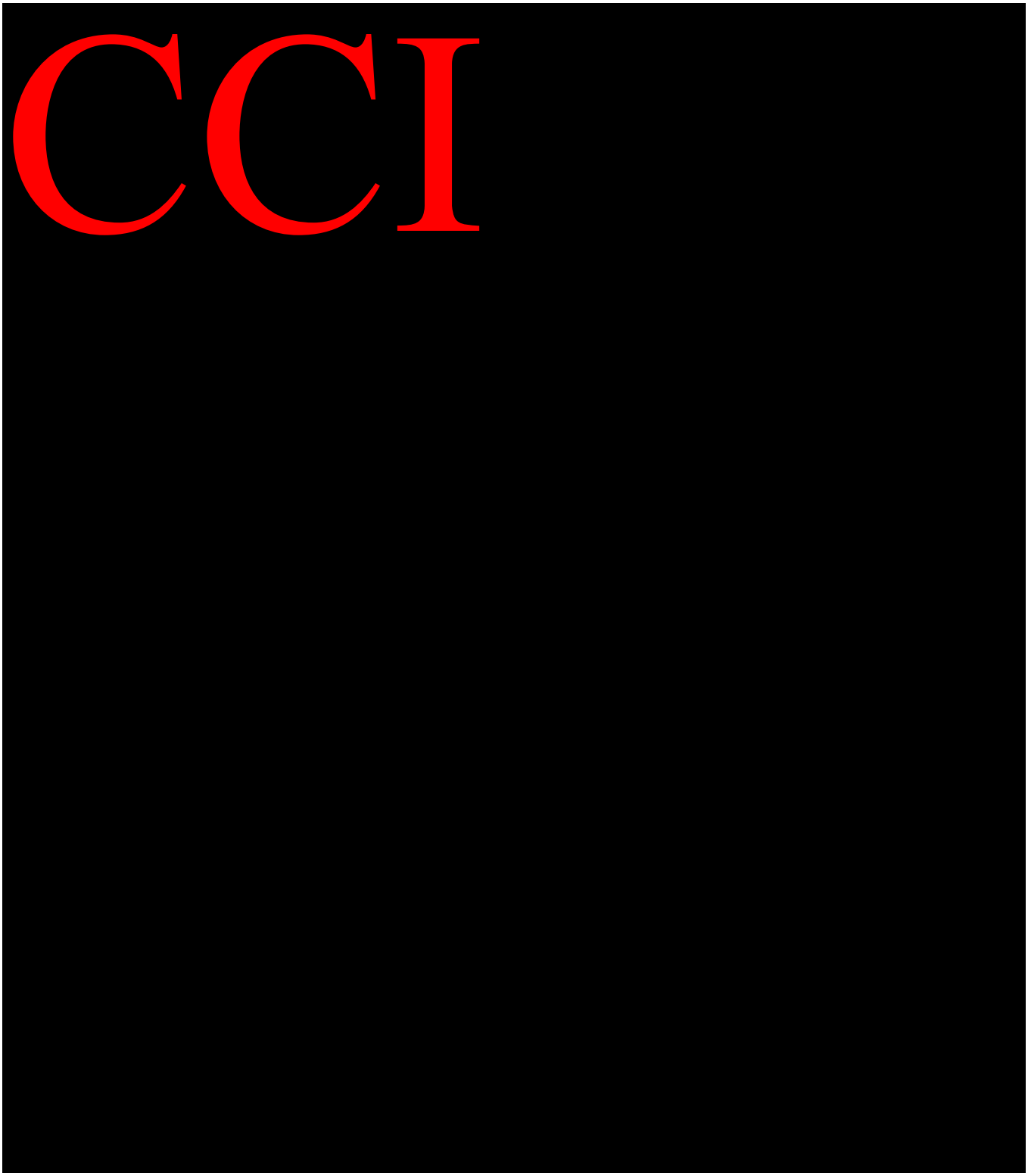
An independent, external, and multidisciplinary data safety monitoring committee (DSMC) CCI [redacted] The DSMC will operate according to a prespecified charter and make recommendations on study conduct related to patient safety. CCI [redacted]

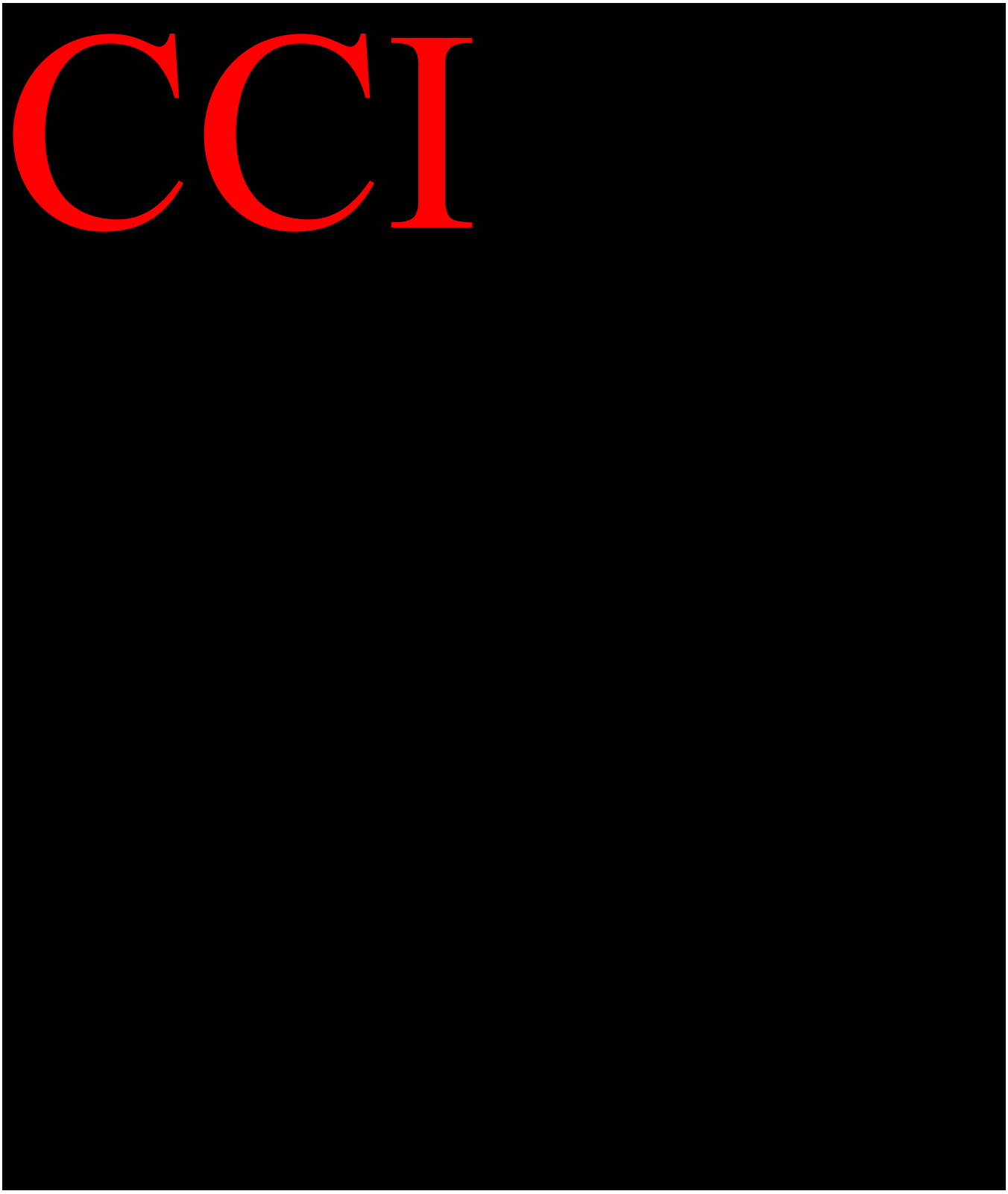
CCI [redacted]


CCI


CCI

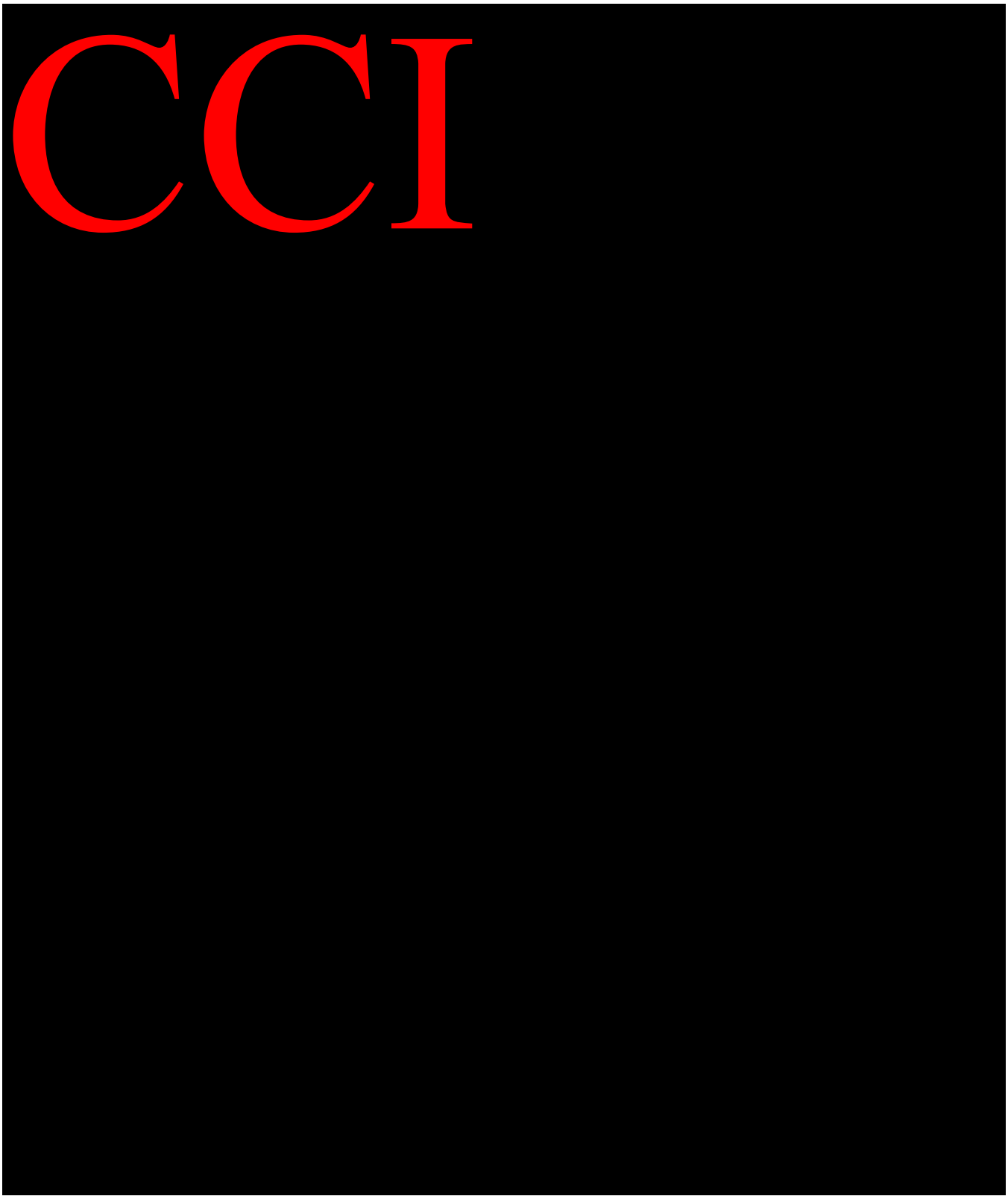

CCI


CCI


CCI


CCI


CCI


CCI


CCI

10.0 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

Below are changes of this plan from Nektar Therapeutics Protocol 18-255-01 "A Phase 2/3, randomized, double blind, placebo-controlled, multi-center study of NKTR-255 vs placebo following CD19-directed CAR-T cell therapy in patients with relapsed/refractory large B-cell lymphoma", protocol amendment 1.0 dated 08 October 2022.

- All protocol deviations are the reasons for such deviations are to be documented and reported to the Sponsor promptly.

11.0 REFERENCES

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059.

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in medicine. 2008;27(13):2420-39.

Ying Z, Song Y, Zhu J. Effectiveness and Safety of Anti-CD19 Chimeric Antigen Receptor-T Cell Immunotherapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma: A Systematic Review and Meta-Analysis. Front Pharmacol. 2022 Apr 25; 13:834113.

Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat Med. 1995;14(4):357-379.

Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management

of cytokine release syndrome. Blood. 2014;124(2):188–195.

Mosteller RD. Simplified Calculation of Body Surface Area. N Engl J Med. 1987 Oct 22;317(17):1098.

DocuSign

PPD

PPD

PPD

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction, and agree to these terms and conditions, please confirm your agreement by clicking the 'I agree' button at the bottom of this document.

Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	Final release versions of Internet Explorer® 6.0 or above (Windows only); Mozilla Firefox 2.0 or above (Windows and Mac); Safari™ 3.0 or above (Mac only)
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	Allow per session cookies

** These minimum requirements are subject to change. If these requirements change, you will be asked to re-accept the disclosure. Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

Acknowledging your access

To confirm to us that you can access this information electronically, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to the terms and conditions described above, please let us know by clicking the 'I agree' button below.

By checking the 'I agree' box, I confirm that:

- I can access and read this electronic consent of ELECTRONIC RECORD AND SIGNATURE DISCLOSURES document; and
- I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and
- In the event of any conflict between the terms of the Electronic Record and Signature Disclosure and the electronically executed agreement, the terms of the electronically executed agreement shall control; and
- I hereby agree that any agreements which are executed electronically through this account when executed and delivered shall be a legally-binding document that will have the same effect as physical delivery of the paper document bearing the original signature. I hereby agree that I have the power and authority of my company to execute and deliver this document on behalf of my company.