Statistical Analysis Plan Version 1.0 19-255-03

A PHASE 1B/2, OPEN-LABEL, MULTICENTER, DOSE ESCALATION AND DOSE EXPANSION STUDY OF NKTR-255 MONOTHERAPY OR IN COMBINATION WITH CETUXIMAB AS A SALVAGE REGIMEN FOR SOLID TUMORS

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Nektar Therapeutics

STATISTICAL ANALYSIS PLAN

A PHASE 1B/2, OPEN-LABEL, MULTICENTER, DOSE ESCALATION AND DOSE EXPANSION STUDY OF NKTR-255 MONOTHERAPY OR IN COMBINATION WITH CETUXIMAB AS A SALVAGE REGIMEN FOR SOLID TUMORS

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
CCI	[redacted]
AE	Adverse Event
CCI	[redacted]
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BLRM	Bayesian logistic regression model
BMI	Body Mass Index
BOR	Best Overall Response Rate
C1D1	Cycle 1 Day 1
CC	Cervical Cancer
CBR	Clinical Benefit Rate
CI	Confidence Interval
CL/calCrCL	Calculated Creatinine Clearance
CM	Concomitant Medication
C_{max}	Maximum Peak Concentration
CnDn	Cycle n Day n (e.g., Cycle 1 Day 1 = C1D1)
CR	Complete Response
CRC	Colorectal Carcinoma or Colorectal Cancer
CRF	Case Report Form
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CCI	[redacted]
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
DSMC	Data Safety Monitoring Committee
EC50	Half Maximal Effective Concentration (EC_{50})
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EWOC	Escalation With Overdose Control
FDA	Food and Drug Administration
FIH	First in Human
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
hr	Hour
IRT	Interactive Response Technology

Abbreviation or Term	Definition
mAb	Monoclonal Antibody
MTD	Maximum Tolerated Dose
NA	Not Applicable
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamic(s)
PD1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
PEG	Polyethylene Glycol
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
q21d	Every 21 Days
q28d	Every 28 Days
QTcB	Corrected QT interval using Bazett formula
QTcF	Corrected QT interval using Fridericia formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
R/R	Relapsed or Refractory
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFU	Survival Follow-up
sIL-15Rα	Soluble IL-15 Receptor Alpha
SOP	Standard Operating Procedure
SRC	Safety Review Committee
TEAE	Treatment Emergent Adverse Event
TP	Total Protein
TTR	Time to Response
TRTSDT	Treatment Start Date
ULN	Upper Limit of Normal
WBC	White Blood Cell

1.0 ADMINISTRATIVE STRUCTURE

This study will be managed via partnership between Nektar Therapeutics and a contract research organization (CRO). Central clinical laboratories will be used for processing of safety specimens, CCI [redacted] pharmacokinetic (PK), CCI [redacted] samples. An interactive response technology (IRT) service provider will manage the patient enrolment, study drug(s) distribution and inventory management. Data for this trial will be entered into an Electronic Data Capture (EDC) system, using a Medidata Rave platform. An independent data monitoring committee (DMC) is established to review the safety data on a periodic basis. Response and progression will be determined using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

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 19-255-03 "A Phase 1b/2, open-label, multi-center, dose escalation and dose expansion study of NKTR-255 monotherapy or in combination with cetuximab as a salvage regimen for solid tumors", protocol amendment 2.0 dated 08 October 2021. The purpose of this plan is to describe the statistical analyses according to Section 9.0 of the study protocol along with any additional analyses, specifications or deviations from the protocol planned. Because only Phase 1b patients were enrolled for the study, this plan will focus on Phase 1b part. Any deviations from these guidelines will be documented in the clinical study report (CSR). All analyses will be conducted by Nektar Statistical Programming & Analysis (SPA) using SAS® Version 9.4 or later.

3.0 STUDY OBJECTIVES

This section shows planned primary, secondary, CCI [redacted] from the study protocol. CCI [redacted]

3.1 Primary Objectives

Phase 1b (Dose Escalation):

To evaluate the safety, tolerability, as well as define the MTD and/or RP2D, of NKTR-255 in combination with cetuximab in relapsed or refractory (R/R) head and neck squamous cell carcinoma (HNSCC) CCI [redacted].

CCI [redacted]

- [redacted]
- [redacted]

3.2 Secondary Objectives

- To evaluate the efficacy of NKTR-255 monotherapy in R/R cSCC, ASCC, and cervical cancer by assessing the ORR by RECIST 1.1
- To evaluate the efficacy of NKTR-255 in combination with cetuximab and NKTR-255 monotherapy by assessing progression-free survival (PFS) and overall survival (OS)

CCI [redacted]

4.0 STUDY ENDPOINTS

This section shows planned primary, secondary, and exploratory endpoints which are related to Phase 1b only.

4.1 Primary Endpoints

- Incidence of dose limiting toxicity (DLT), treatment emergent adverse events (AEs) in Phase 1b

4.2 Secondary Endpoints

- ORR by investigator assessment (per RECIST 1.1) in R/R cSCC, ASCC, and cervical cancer
- PFS and OS in NKTR-255 monotherapy and in combination with cetuximab


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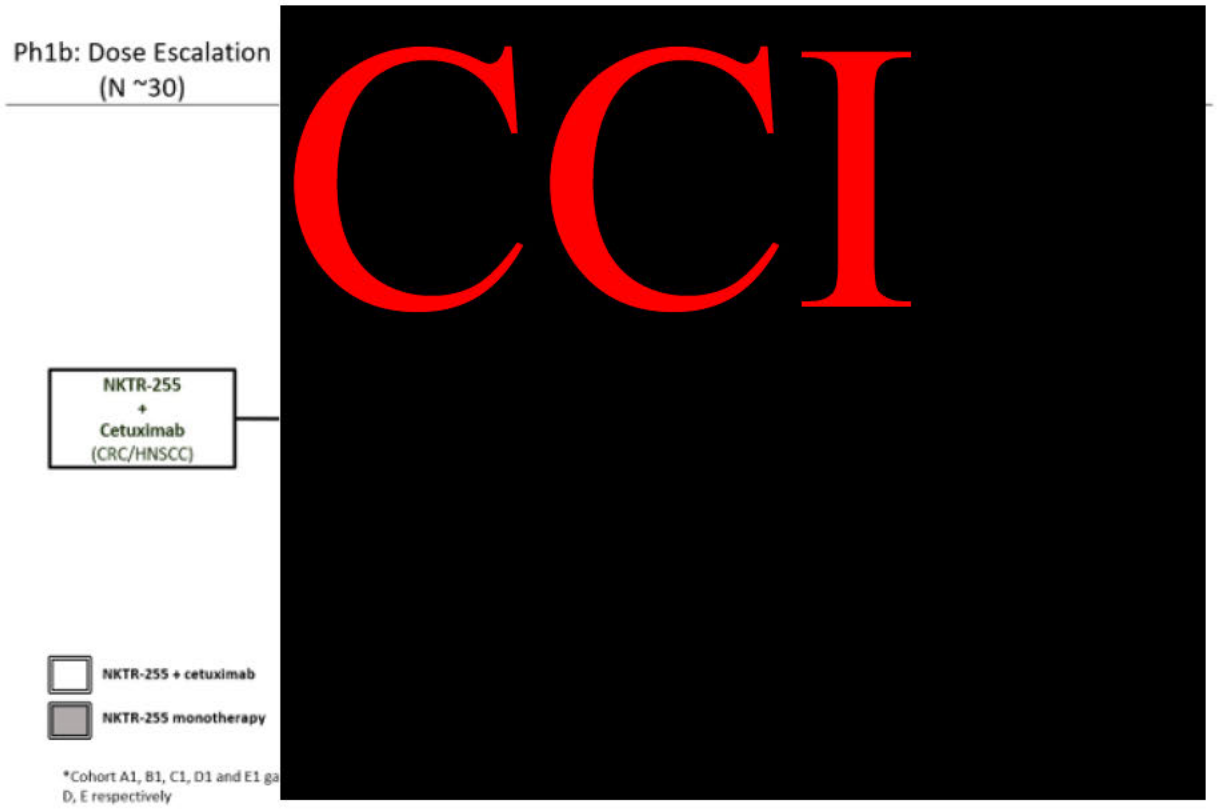
5.0 OVERALL STUDY DESIGN AND PLAN

This study is a Phase 1b/2, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-255 in patients with R/R HNSCC, CRC, CCI . This section shows the planned study design including CCI Phase 1b CCI in the protocol. Because no Phase 2 patients were enrolled in the study, this plan will focus only on analyses for the Phase 1b part.

Figure 1: Study Schema



CCI CRC = colorectal cancer; CCI HNSCC = head and neck squamous cell carcinoma; Ph = Phase; RP2D = recommended Phase 2 dose

Note: No intra-patient dose escalation will be conducted in any cohort.

Note: The dose-limiting toxicity (DLT) window for NKTR-255 in combination with cetuximab is 21 days following the initial dose of NKTR-255.

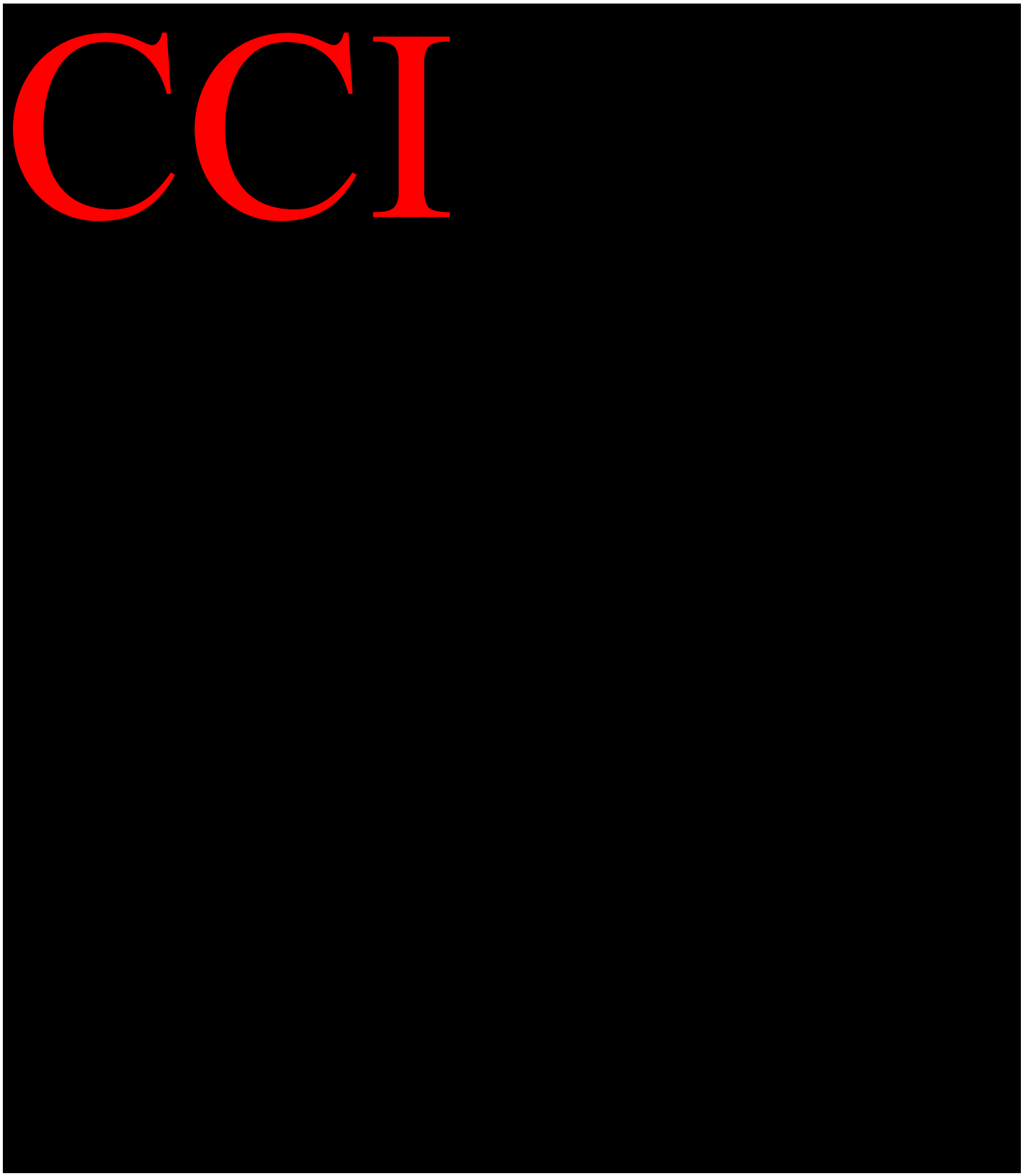
Phase 1b – Dose Escalation

The NKTR-255 starting dose will be 1.5 μg/kg, which had no safety concerns as defined by pre-specified dose limiting toxicities in the first cohort of the first-in-human (FIH) study Protocol 18-255-02. The starting dose is based on the safety data generated from the escalation cohorts and the RP2D determination from the FIH study. The starting dose will not be greater than the highest dose determined by the Safety Review Committee (SRC) to have no safety concerns in the FIH study.

After an initial cetuximab loading dose, patients will receive IV NKTR-255 every 21 days (q21d) in combination with cetuximab weekly. Beginning with Dose Level 1, successive cohorts of at least 3 patients each will receive ascending doses of NKTR-255 until the MTD and/or RP2D is determined. Approximately 30 patients may be enrolled in the dose escalation phase of the study. A 2-parameter Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle (Neuenschwander, 2008) will be used as a guide during the escalation phase of the study for dose level selection and for determination of the MTD and/or RP2D. Additional dose levels may also be opened to further explore the MTD and/or RP2D.

The first patient (a sentinel patient) of each escalating NKTR-255 dose level will be monitored for safety and tolerability for 7 days after the first dose of NKTR-255 before additional patients are dosed within the same dose level. A composite of clinical information will be used to select the RP2D based on safety and tolerability, PK, CCI and optimal biological response. Additional patients may be enrolled to refine the RP2D, and a minimum of 6 patients will be required to define the RP2D

The dose limiting toxicity (DLT) window is 21 days after the first dose of NKTR-255. Patients who achieve optimal response (partial response [PR] or complete response [CR] as determined by RECIST 1.1) after at least 1 tumor assessment, as determined by the Investigator and in consultation with the Medical Monitor, will be given the option to continue treatment with NKTR-255 as single agent for maintenance every 28 days (q28d) at the same dose as the patient's originally assigned dose.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- Intermediate doses may be evaluated.
- No intra-patient dose escalation will be allowed.
- Enrollment into a new dose level with an escalating dose of NKTR-255 cannot begin until the DLT window has closed for the last patient in the prior dose cohort. The DLT window is 21 days after the first dose of NKTR-255.
- The SRC will assess safety before opening dose escalation to the next level.
- The Sponsor's decision to declare the RP2D of NKTR-255 can occur at any given dose level prior to reaching the MTD based on safety, PK CCI .
- Data from a minimum of 6 evaluable patients are required to define the RP2D.
- Dose reduction of NKTR-255 is not allowed during dose escalation within the DLT window. Outside of the DLT window in the dose escalation phase, and during dose expansion, dose levels of NKTR-255 may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested (the dose level may be de-escalated in order to characterize RP2D for a specific cohort).
- The cetuximab dose may be reduced or adjusted based on review of available safety and tolerability data. Dose adjustment or discontinuation for cetuximab may be required based on emerging toxicities and should follow the guidelines specified in the protocol and in the current Prescribing Information for Erbitux® (cetuximab).


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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 during the dose escalation phase will be presented by dose level groups and overall. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. The means will be presented to one decimal place beyond which the data were captured. The standard deviation will be presented to two decimal places beyond which the data were captured. The minimum and maximum will be presented to the precision with which the data were captured.

Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. A row or column denoted 'Missing' will be included in count tabulations where necessary to account for dropouts and missing values. Percentages will be rounded to 1 decimal place and the percent will be suppressed when the count is zero. The denominator will be the number of subjects in the cohort of interest unless otherwise noted.

Unless specified otherwise, all 95% confidence interval for proportions will be two-sided and be based on the exact (Clopper-Pearson) method and confidence interval for the quartiles of time to event variables will be based on the Brookmeyer and Crowley method using log-log transformation (1982).

For analyses by visit, only data of scheduled visits will be reported, and nominal visits will be used. For analyses up to a certain time point, data of both scheduled visits and unscheduled visits up to that time point will be considered. For analyses of worst post-baseline value, both scheduled and unscheduled measurements will be included.

For BOR and PFS, both scheduled and unscheduled assessments will be included. The actual investigator response assessment dates will be used.

6.2 Determination of Sample size

6.2.1 Sample Size Determination in Phase 1b

This is a Phase 1b/2 dose escalation and dose expansion study. During dose escalation (Phase 1b), successive cohorts of at least 3 patients will be treated at each dose level until the MTD and/or RP2D is determined. A 2-parameter adaptive Bayesian Logistic Regression Model (BLRM) with overdose control (EWOC) similar to that proposed by Babb et al. (1998) will be used to guide dose escalation in this study. After the completion of the DLT observation period of the last patient enrolled in a dose escalation level, the BLRM will be re-run to obtain updated posterior probabilities of under-dosing, targeted toxicity, and excessive toxicity (see Appendix 1 of Protocol Amendment 2.0) for all doses.

The dose recommended by the adaptive Bayesian logistic model will be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of the analysis in determining the next dose level to be investigated. Generally, the study will not treat patients at a dose higher than the model-recommended dose. However, the study may escalate to or stay at a dose higher than the model-recommended dose if such a decision is consistent with accepted clinical practice (eg, standard 3+3 escalation rules serving as guidance). The dose given to the next dose level in the study will be based on considerations of the MTDs estimated by the BLRM. The overall clinical assessment of all available safety and tolerability, PK, and PD data may also be taken into consideration for the determination of dose given to the next dose level.

Additional patients may be added to each cohort based on the scheme and rules outlined in protocol Section 5.2.3.4 or Sponsor determination of the need for additional data to further evaluate the benefit/risk profile. CCI

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6.3 Analysis Populations

Enrolled Population: All patients who receive at least 1 dose (or partial dose) of cetuximab or NKTR-255.

Safety Population: All patients who receive at least 1 dose (or partial dose) of NKTR-255.

Cetuximab-only Population: All patients who receive at least 1 dose (or partial dose) of cetuximab but without any dose of NKTR-255.

DLT Population: All patients who receive at least 1 dose of the combination treatment of NKTR-255 and cetuximab and who complete the DLT observation period or discontinue from

the study treatment due to a DLT will be included, where DLT window is 21 days since the first dose of NKTR-255.

Response-evaluable Population: The Response-evaluable Population is defined as patients who have measurable disease (per RECIST 1.1) at baseline, receive at least 1 dose (or partial dose) of NKTR-255, and have at least 1 post-baseline assessment of tumor response.

Pharmacokinetic Population: All patients in the Safety Population who receive at least 1 dose of treatment and have at least one evaluable PK concentration.

CCI [redacted]

CCI [redacted]

6.4 Handling of Missing Data

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

Missing baseline data will not be imputed. This includes variables which are not allowed to be collected according to local regulations (e.g. race in France).

For post-baseline data, observations with values ‘not done’, ‘not evaluable’, ‘not applicable’ will be treated as missing values. For descriptive analyses, missing values will not be imputed. Number and percentage of missing values will be described separately. For analyses involve modeling, handling of missing values will be explicitly specified.

Detailed approaches for the imputation of missing information in death dates, AE start and end dates, cancer history diagnosis dates, and prior and concomitant medications start, and end dates are described below. Missing dates for surgery or procedures will use the same rules as for concomitant medications.

The general approach to handle partial dates are as follows:

- Dates with missing year information will not be imputed.
- Dates with missing month or day information will be imputed. Conservative imputation approaches will be adopted when applicable. For example, imputation rules for AE start and end dates are designed such that AEs with partially missing start dates will be included as TEAE if available information is not sufficient to decide whether AE starts before C1D1.
- Last known alive date, C1D1, the end of study follow-up date, informed consent date, etc. are used as reference dates to guide the imputation when applicable.

1) For the subsequent anti-cancer therapy start date:

   - If only the day is missing then: if the end date of the subsequent anti-cancer therapy is complete, impute to the minimum of (the last day of the month, end date of subsequent anti-cancer therapy); otherwise impute to the last day of the month.
   - If the month or year is missing, then leave missing.

2) For time from diagnosis of disease to treatment start date (TRTSDT), partial dates for initial diagnosis and diagnosis of disease will be imputed as follows:

Table 2: Partial Dates Imputation Rules for Initial Diagnosis and Diagnosis of Disease

Parameter	Missing	Additional Conditions	Imputation
Initial Diagnosis Date	D	M and Y the same as M and Y of first dose date of study drug	Date of the first day of month of TRTSDT
		M and/or Y not same as first dose date of study drug	Day 15 of the month of diagnosis
	D and M	Y the same as Y of first dose date of study drug(s)	Date of the first day of month of TRTSDT
		Y prior to Y of first dose date of study drug	01 July of the year of diagnosis
	D, M and Y	None	No imputation

3) Partial or missing dates for Concomitant Medication

   - If missing the day and/or month of the start date, the medication will not be considered as concomitant if the month and/or year of the start date is after the last dose date + 30 days or (date of initiation of subsequent anti-cancer therapy -1 day), whichever is earlier
   - If missing day and/or month of the stop date, the medication will not be considered as concomitant if the month and/or year of the stop date is prior to C1D1
   - A medication with completely missing start and end dates will be classified as concomitant.

4) For death date, the following conventions will be used:

   - If the death date is completely missing but reason for death is present, it will be imputed as the last known alive date

- If the death date is partially missing (missing day only, or missing both day and month), the death date and corresponding last known alive date will be imputed in 2 steps:
  - 1. Imputed as the 1st of the month (missing day only) or January 1st of the year (missing both day and month)
  - 2. The imputed death date from step 1 will be compared to the latest alive date captured from multiple sources (unimputed), and the later of the two will be considered as the imputed death date and last known alive date

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

Run-in period:

Eligible patients on combination therapy will receive cetuximab 400mg/m^2 IV as a loading dose during the study run-in period (Day -7). The run-in period therefore starts from the time the patient receives cetuximab and ends when the patient receives combination treatment of NKTR-255 +cetuximab.

Study drug or study treatment: Study drug or study treatment refers to NKTR-255 or cetuximab.

Study day: Study Day 1 (C1D1) is the first day that the combination treatment of NKTR-255 +cetuximab begins.

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.

Last known alive date: The date of last known alive date will be derived for patients unknown to have died or known alive at the analysis cut-off by using following dates:

- Patient assessment dates (blood draws CCI [redacted], vital signs, performance status, ECG, tumor assessments, ECOG, or tumor biopsy dates)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation
- AE start or end date
- Concomitant medication start or end dates
- Last date of contact collected on the 'Survival follow-up' eCRF (do not use date of survival follow-up assessment unless status is 'alive')
- Study treatment start or end date
- Date of discontinuation for study participation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up)

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used.

End of Study: End of study is defined as no more than 2 years after the last patient received his or her last dose of NKTR-255 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.

NKTR-255 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.

Extended treatment-emergent adverse events (TEAE) period: Start of any study drug through 60 days post last dose of study drug, or until a new antineoplastic regimen has been initiated, whichever comes first.

Prior medications: Prior medications are defined as medications with start date prior to C1D1.

Concomitant medications: Concomitant medications are defined as 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. Medications with a start date after the initiation of any subsequent anticancer treatment will not be considered concomitant medications.

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

Best overall response (BOR): The BOR is defined as the confirmed best response designation over post-baseline response assessments. Disease assessments beyond progression or after start of subsequent therapy will not be considered for BOR.

Overall response rate (ORR): The ORR is defined as the proportion of subjects who have achieved PR or better as their BOR.

Complete response rate (CRR): The CRR is defined as the proportion of subjects who have achieved CR as their BOR.

Responders: Responders are defined as subjects with a confirmed BOR of PR or better. Ongoing responders are defined as responders who have not progressed, not died, not been off study and not started a subsequent therapy.

Duration of response (DOR): DOR is defined as the time from first response (PR or better) to the date of disease progression or death due to any cause, whichever occurs first. Subjects who remain alive and have not progressed are censored on the last evaluable disease assessment date (prior to subsequent cancer therapy). Same censoring rules for PFS apply to DOR. This endpoint is only defined for subjects with a confirmed BOR of PR or better.

Time to response (TTR): TTR is defined as the time from treatment start date (i.e. first dose of Cetuximab) to first response (PR or better). This endpoint is only applied for subjects with a confirmed BOR of PR or better.

Progression free survival (PFS): The PFS is defined as the time between the first dose date of Cetuximab to the date of disease progression or death, whichever is earlier. For patients without PD or death, those patients will be censored following the rules specified below.

Table 3: PFS Censoring Rules

Situation	Date of Disease Progression or Censoring	Outcome
No post-baseline tumor assessments and no death	first dose date of Cetuximab	Censored
No progression and no death, and no new anti-cancer therapy started	Date of last assessment showing no evidence of disease progression	Censored
New anti-cancer therapy started without progression before	Date of last assessment before the start of anti-cancer therapy showing no evidence of disease progression	Censored
Disease progression reported on one or multiple response assessments without new anti-cancer therapy before	Date of earliest evidence of PD	Progressed
Death without PD or new anti-cancer therapy before	Date of death	Death
Two or more consecutive missing tumor assessments, and no progression before the missing assessment	Date of the last assessment prior to the missing assessment showing no evidence of disease progression	Censored

Overall Survival (OS): OS is defined as the time from the first dose date of Cetuximab to death from any cause. Patients will be followed until their date of death, loss to follow-up, or withdrawal of consent for further follow-up for survival, regardless of the start of anti-cancer therapy. Patients who are lost to follow-up will be censored at their last date known to be alive. 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 first dose date of Cetuximab will be censored on the first dose date of Cetuximab.

7.0 STATISTICAL ANALYSIS

Starting from this section, this statistical analysis plan will only focus on Phase 1b part of the study where patients were enrolled.

7.1 Patient Disposition

The summary for subject disposition will include number of subjects enrolled in the dose escalation phases, number of subjects in each study population, number of subjects who discontinue from study treatment and reason for treatment discontinuation, and number of subjects who discontinue from study and reasons for study discontinuation.

All patients in enrolled population will be included in the summary table, additional summary tables will be generated for HNSCC and CRC enrolled population separately. All disposition data will be presented in a data listing.

7.2 Protocol Deviations

Protocol deviations will be classified as significant/major or non-significant/minor 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 Demographic and Other Baseline Disease Characteristics

Demographic and baseline characteristics will be summarized and listed for the safety population, additional summary tables will be generated for HNSCC and CRC safety population separately.

Demographic variables include the following:

- Age
- Age categorization I (< 65, ≥ 65 years)
- Age categorization II (<65, ≥ 65 and < 75, ≥ 75 years)
- Age categorization III (<65, ≥ 65 and < 75, ≥ 75 and <85, ≥ 85 years)
- Sex
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Unknown, Race not reported)

Baseline characteristics include:

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

7.3.2 Cancer History and Prior Cancer Treatment

The following prior cancer history and cancer treatment history will be summarized and listed for HNSCC and CRC safety population separately.

Table 4: Cancer History and Prior Cancer Treatment

Cancer Type	Parameters
All	• Time from initial primary cancer diagnosis to first dose of NKTR-255 (months) • Stage at initial diagnosis • Stage at most recent recurrence • Current status • Number of lines of prior systemic cancer therapy • Time since start of most recent line of systemic cancer therapy • Best response of most recent line of systemic cancer therapy • Sites of metastasis • EGFR Mutational Status • Prior EGFR experience • Prior PD-1/L1 experience
HNSCC	• Histological type • Human papillomavirus infection (HPV) status • Epstein-Barr virus (EBV) status • P16 status • PD-L1 combined positive score (CPS)
CRC	• History of brain metastases • Mutational status (BRAF status, NRAS/KRAS Status) • MSI status

7.3.3 Surgical History and Prior Radiotherapy

The number and percent of patients who had prior cancer-related surgery will be summarized by type of surgery.

The number and percent of patients who had prior radiotherapy will be summarized by site of radiotherapy.

All prior radiotherapy and cancer related surgery history will be listed.

7.3.4 Medical History

Medical history collected at screening will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for HNSCC and CRC safety population separately. For summary tables, patient will be counted only once within each SOC and PT. All medical history will also be provided in a listing

7.4 Treatments and Medications

7.4.1 Prior and Concomitant Medications

Prior and concomitant medications will be coded by the World Health Organization Drug Dictionary Enhanced (WHODrug) using Anatomical Therapeutic Chemical (ATC) level 2 term and preferred Term (PT). The number and percentage of subjects who have received each prior medication and who have received each concomitant medication will be summarized by ATC level 2 term and PT. Subjects 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 and Sections 6.4.

All prior and concomitant medications will be listed.

7.4.2 Subsequent Anti-Cancer Therapy

Subsequent cancer therapy will be coded by the WHODrug using ATC level 2 term and PT. The number and percentage of subjects who have subsequent cancer therapy will be summarized by ATC level 2 term and PT. Subjects will be counted only once under each ATC level 2 term and preferred term.

All subsequent cancer therapy will be listed.

7.4.3 Study Drug Exposure and Dose Modification

The number and percentage of subjects with at least one dose delays, dose reductions, and dose interruptions, and the reasons will be summarized respectively for HNSCC and CRC safety population.

The following variables will also be summarized for NKTR-255 and cetuximab respectively for HNSCC and CRC safety population:

- Exposure duration (days): Date of last administration – date of first administration +1, regardless of any delay of dosing between the first and the last dose.
- Actual number of infusions: Total number of infusions for which the patient received non-zero doses.
- Planned number of infusions: The cycle number for which the patient received last non-zero doses.
- Cumulative dose (ug): The summation of actual dose a patient received across all cycles. The units ug/kg used for NKTR-255 and mg/m^2 for cetuximab.
- Average dose per infusion (ug): Cumulative dose / Actual number of infusions.

All study exposure summary data will be presented in a data listing.

7.5 Efficacy Analysis

Tumor response will be evaluated using RECIST 1.1 criteria (Eisenhauer, 2009). Tumor burden will be characterized prior to enrollment, and response assessments will be at approximately every 9 weeks starting from C1D1. A confirmed BOR of CR or PR requires the confirmation occurring at least 4 weeks after initial documentation. A BOR of SD requires a minimum of 63 days on study from C1D1 to the date of the first imaging assessment., Disease assessment 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 subjects. However, tumor assessment beyond progression will not be considered for response endpoints.

For efficacy endpoints including ORR, CBR, BOR summary will be based on the response-evaluable population. DOR and TTR will be summarized among confirmed responders. PFS, OS will be analyzed in the safety population. In addition, swimmer plot of tumor response and waterfall plot of best tumor size change will be generated based on safety population. Separate summary table and figures for efficacy analyses will be generated for HNSCC and CRC patients.

7.5.1 Best Overall Response, Objective Response Rate, Clinical Benefit Rate

BOR will be summarized by response category. Number and percentage of subjects who achieved CR, or PR (ORR) and who achieved CR, PR or SD (CBR) will the summarized with 95% CIs.

7.5.2 Duration of Response and Time to Response

The DOR will be summarized for subjects who achieve confirmed PR or better determined by investigators. 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 subjects who have events or censored will also be presented. Among the responders, subjects 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 will also be provided for responders. A listing instead of summary tables may be provided for DOR and TTR if there are not sufficiently large number of confirmed responders.

7.5.3 Progression Free Survival (PFS)

PFS will be analyzed in the safety population. Investigator-assessed PFS will be summarized descriptively using the Kaplan-Meier (KM) product-limit method. KM estimate of PFS rates at 6, 9 and 12 months will be calculated. PFS rates at 18, and 24 months may also be estimated depending on whether minimum follow-up will be longer than timepoint to generate the rate. 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 analyzed in the safety population. OS will be summarized descriptively using the Kaplan-Meier (KM) product-limit method. KM estimate of OS rates at 6, 9 and 12 months will be calculated. OS rates at 18, and 24 months may also be estimated depending on whether minimum follow-up will be longer than timepoint to generate the rate. 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 Subgroup Analysis

No subgroup analysis is planned for efficacy endpoints other than summarizing separately for HNSCC and CRC patients.

7.6 Safety Analyses

Unless otherwise specified, all safety analyses except for incidence of DLTs will be based on the Safety Population. All summaries will be provided by dose groups in Phase 1b.

7.6.1 Dose Limiting Toxicities

DLTs will be evaluated in the DLT evaluation window of 21 days following NKTR-255 administration in Cycle 1 Day 1 as specified in the protocol. Delayed DLTs are AEs that meet criteria of DLT defined in the protocol but occur after the DLT evaluation window. DLTs and delayed DLTs will be summarized separately by system organ class (SOC) and preferred term (PT) in the DLT population. All DLTs and delay DLTs will be listed by patient.

7.6.2 Adverse Events

Verbatim AE terms on case report forms will be mapped to PTs and SOCs using the Medical Dictionary for Regulatory Activities (MedDRA) (version 22.0). CRS events are graded based upon ASBMT 2018 criteria. All other Adverse Events and toxicity will be evaluated according to CTCAE Version 5.0.

TEAEs will be summarized by SOC, PT, 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.

TEAE period defined in Section 6.6.1 will be applied if AEs are summarized in safety population, extended TEAE period will be applied if AEs are summarized in enrolled population. All AE tables by worst CTCAE grade will includes 4 categories, which are Grade 1-2, Grade 3-4, Grade 5 and all Grades.

The following AE summaries will be provided in safety population with NKTR-255 TEAE period

- Overall summary of TEAEs
- TEAEs by SOC, PT and Worst CTC Grade
- Grade 3 and above TEAEs by SOC and PT
- TEAE Related to NKTR-255 by SOC, PT and Worst CTC Grade
- Serious TEAE by SOC, PT and Worst CTC Grade
- Serious TEAE Related to NKTR-255 by SOC, PT and Worst CTC Grade
- Grade 3 and above TEAEs related to NKTR-255 by SOC and PT
- TEAE Leading to NKTR-255 Dose Delay by SOC and PT
- TEAE Leading to NKTR-255 Dose Reduction by SOC and PT
- TEAE Leading to NKTR-255 Dose Interruption by SOC and PT
- TEAE Leading to Discontinuation of NKTR-255 by SOC and PT
- TEAE Leading to Death by SOC and PT

Other safety observations (OSO) will be summarized in following categories:

- AEs associated with increased cytokine levels in blood
    - Arthralgia
    - Asthenic conditions/Fatigue
    - Flu like symptoms

  - Elevated hepatic transaminases
  - Hypotension
  - Rash and pruritus
- Cytokine release syndrome (CRS)
- Elevated hepatic transaminase
- ICANs (this is an individual PT which is Immune Effector Cell-Associated Neurotoxicity Syndrome and is included in TEAE summary tables)
- Infections
- Infusion related reaction (IRR, 48-hour window post NKTR-255 administration)
- Neutropenia
- QT/QTc Prolongation
- Thrombocytopenia

For IRR (except for the PT of infusion related reaction), events that start within 48 hours after NKTR-255 drug administration will be included. If AE onset time is available, the time information will be used to exclude events that start before dosing and include events that start on day 3 relative to dosing day but within 48 hours of start of NKTR-255 administration; otherwise, AEs that start on the same and next day of dosing will be included. Analysis on IRR will only be performed for patients who receive at least one NKTR-255 dose.

The following summaries will be performed for OSO using safety population with TEAE period. A listing of how OSO is categorized will also be provided.

- Treatment-emergent Other Safety Observations (OSO) by Category/PT and Worst CTC Grade
- Grade 3 and above Treatment-emergent Other Safety Observations (OSO) by Category/PT
- Treatment-emergent Other Safety Observations (OSO) Related to NKTR-255 by Category/PT and Worst CTC Grade
- Serious Treatment-emergent Other Safety Observations (OSO) by Category/PT and Worst CTC Grade
- Serious Treatment-emergent Other Safety Observations (OSO) Related to NKTR-255 by Category/PT and Worst CTC Grade

Additionally, site identified Treatment-emergent CRS events will also be summarized and listed by PT and Worst CTC Grade.

The following AE summaries will be provided in enrolled population with extended TEAE period:

- Overall summary of Extended TEAEs
- Extended TEAE Related to any Study Drug by SOC, PT and Worst CTC Grade
- Serious Extended TEAE Related to any Study Drug by SOC, PT and Worst CTC Grade
- Grade 3 and above Extended TEAEs related to any Study Drug by SOC and PT
- Extended TEAE Leading to Discontinuation of any Study Drug by SOC and PT
- Extended TEAE Leading to death by SOC and PT

The following data listings will be provided in enrolled population:

- All TEAEs
- Serious TEAEs
- Grade 3 or Higher TEAEs
- Other Safety Observations (OSO)
- TEAEs Leading to Study Drug Discontinuation
- TEAEs Leading to Dose delay, Reduction, and Interruption
- TEAE leading to death

7.6.3 Death

All cause deaths will be summarized by dose level in the enrolled population:

- All deaths, reasons for death
- Deaths within treatment-emergent period, and reasons for death
- Deaths within extended treatment-emergent period, and reasons for death

A by-patient listing of deaths will be provided for all enrolled patients.

7.6.4 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 after the last dose of NKTR-255, but before the initiation of subsequent anticancer treatment.

Below are the selected laboratory parameters with the direction of interest to be summarized:

7.6.4.1 Hematology

- Absolute neutrophil count (ANC) (Decrease)
- Hemoglobin (Hgb) (Both directions)
- Hematocrit (HCT) (Both directions)
- Platelet count (Decrease)
- White blood cell (WBC) count (Both directions)
- Lymphocyte count (Both directions)

7.6.4.2 Chemistry

- AST (Increase)
- ALT (Increase)
- Alkaline phosphatase (ALP) (Increase)
- Albumin (Both)
- Total Bilirubin (TBL) (Increase)
- Creatinine (Increase)
- Blood urea nitrogen (BUN) (Both directions)
- Calcium (absolute, albumin-corrected) (Both directions)
- Gamma-glutamyl transferase (GGT) (Increase)
- Sodium (Both directions)
- Potassium (Both directions)
- Chloride (Both directions)
- Lactate dehydrogenase (LDH) (Increase)
- Lipase (Increase)
- Amylase (Increase)
- Magnesium (Decrease)

A table presenting number and percentage of patients with post-baseline CTC grade increased from baseline (any grade, grade 3-4) will be generated for the above selected laboratory parameters. If lab parameters do not have toxicity grade in CTCAE v5.0, it will not be presented in the table. In addition, a table presenting hepatic impairment evaluation and a table presenting renal impairment evaluation will be generated. The hepatic and renal impairment evaluation criteria can be found below:

- Hepatic impairment evaluation

  Normal: TBL ≤ ULN and AST ≤ ULN

  Mild: ULN < TBL ≤ 1.5 x ULN or AST > ULN

  Moderate: 1.5 x ULN < TBL ≤ 3 x ULN

  Severe: TBL > 3 x ULN

- Renal impairment evaluation based on baseline estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) (Levey et al., 2009)

  Normal: eGFR ≥ 90 mL/min/1.73 m^2

  Mild: eGFR between 60 to 89 mL/min/1.73 m^2 (inclusive)

  Moderate: eGFR between 30 and 59 mL/min/1.73 m^2 (inclusive)

  Severe: eGFR < 30 mL/min/1.73 m^2

- Where $eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]
  - Scr is serum creatinine in mg/dL,
  - κ is 0.7 for females and 0.9 for males,
  - α is -0.329 for females and -0.411 for males
  - min indicates the minimum of Scr/κ or 1
  - max indicates the maximum of Scr/κ or 1
  - age = years

- Renal impairment evaluation based on Cockcroft and Gault equation (calculated creatinine clearance)

  Severe: calCrCL <30

  Moderate: 30 ≤ calCrCL ≤ 59

  Mild/Normal: calCrCL ≥ 60

Where calCrCl (male) = ([140-age] × weight in kg)/(serum creatinine in mg/dL× 72);

calCrCl (female) = calCrCl (male) × 0.85

A listing of patients who met Hy's Law criteria will be provided. Hy's Law criteria are defined as follows:

- ALT >= 3xULN or AST >= 3xULN
- Total bilirubin TBL >= 2xULN
- ALP <= 2xULN or missing

7.6.5 Additional Safety Analyses

7.6.5.1 Vital Signs

Vital signs visits will be included in listings. Vital sign abnormality will be summarized by maximum and minimum post-baseline value. Abnormal values are defined as an absolute value outside the defined range in Table 5.

Table 5: Vital Sign Abnormality Definition

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 160 mmHg	< 90 mmHg
Diastolic blood pressure	> 100 mmHg	< 60 mmHg
Heart rate	> 100 bpm	< 60 bpm
Temperature	> 38ºC	< 35ºC
Respiratory rate	> 24/min	< 12/min

7.6.5.2 Electrocardiogram

ECG (safety) parameters (numeric) will be summarized at baseline. Worst post-baseline and Worse post baseline change from baseline will also be summarized

Categorical outliers will be summarized in frequency tables. ECG finding at any timepoint will be determined as an outlier if the following criteria (which are assessed separately) are met for the ECG intervals (ie, QTcF, PR, QRS, HR).

Table 6: ECG Outlier Criteria

ECG Interval	Categorical Outlier Criteria
QTcF	Male: Treatment-emergent value of > 450 and ≤480 ms when not present at baseline (new onset)
	Male: Treatment-emergent value of > 480 and ≤ 500 ms when not present at baseline (new onset)
	Male:Treatment-emergent value of > 500 ms when not present at baseline (new onset)
	Increase of QTc from baseline of > 30 and ≤ 60 ms
	Increase of QTc from baseline > 60 ms
	Female: Treatment-emergent value of > 470 and ≤ =480 ms when not present at baseline (new onset)
	Female: Treatment-emergent value of > 480 and ≤ = 500 ms when not present at baseline (new onset)
	Female:Treatment-emergent value of > 500 ms when not present at baseline (new onset)
	Increase of QTc from baseline of > 30 and ≤ 60 ms
	Increase of QTc from baseline > 60 ms
PR	Increase of PR from baseline > 25% resulting in PR > 200 ms
QRS	Increase of QRS from baseline > 25% resulting in QRS > 120 ms
HR	Decrease of HR from baseline >25% resulting in HR < 50 bpm
	Increase of HR from baseline >25% resulting in HR > 100 bpm

Number and percentages of categorical outliers will be summarized for each treatment group. A patient will be counted only once for a particular outlier event if the patient experiences more than 1 episode of that event.

7.6.6 Listing of safety ECG Parameters will be Provided. COVID-19 Related Analyses

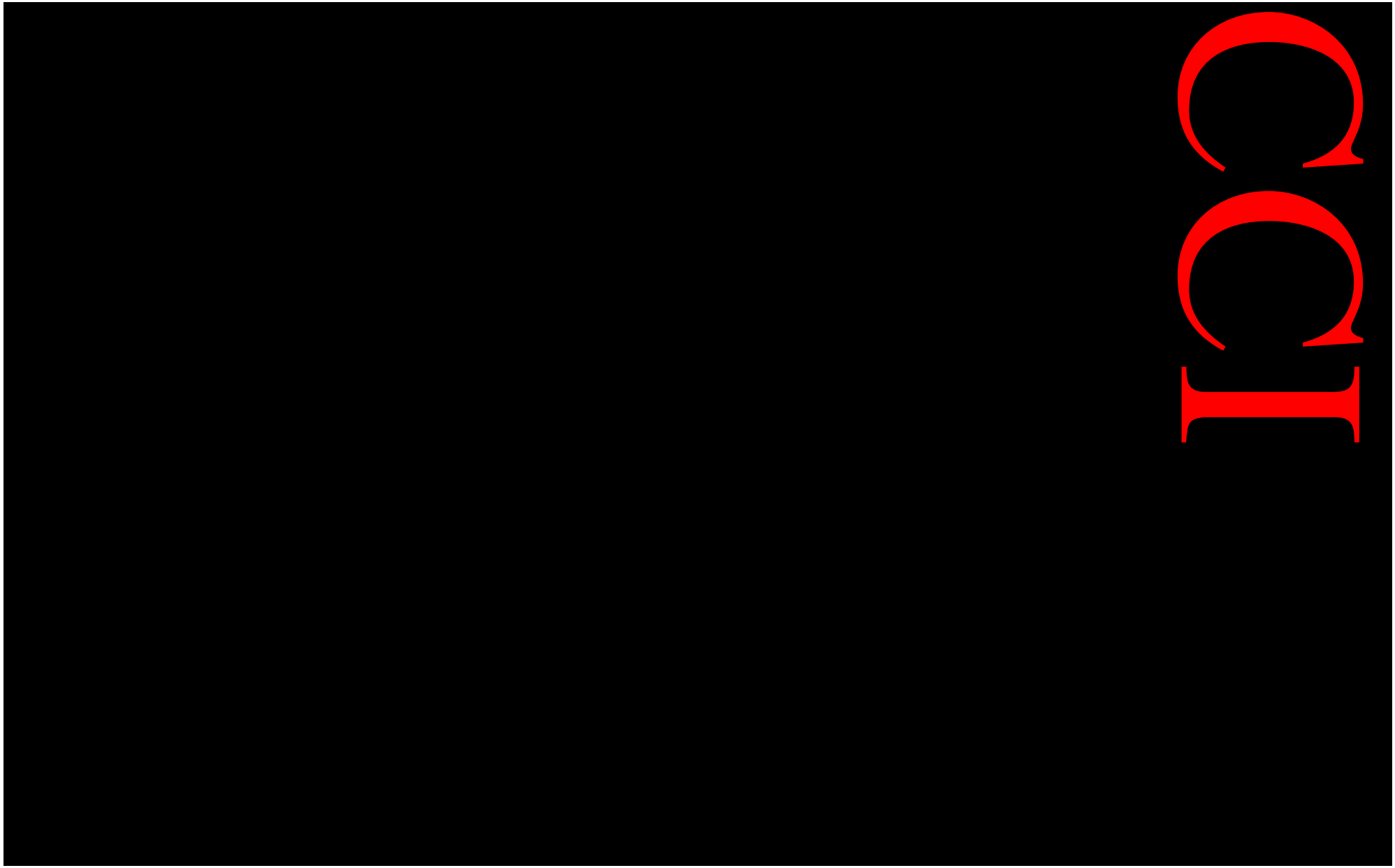
A listing of patients who missed study visit(s) or study procedure(s) due to COVID-19 will be provided.

8.0 DATA MONITORING COMMITTEE AND SAFETY REVIEW

An SRC will be used for the dose escalation and dose expansion phases of the study. The SRC will be comprised of at least one site Investigator and the Sponsor's Medical Monitor. Additional participants may include representatives from the Sponsor's Clinical Development, Drug Safety, Biostatistics, and Clinical Pharmacology divisions as well as other functional representatives as needed to review safety data. For dose escalation cohorts, the SRC will jointly assess safety before opening dose escalation to each level. The exact dose will be confirmed based on review of safety data after a minimum of 3 patients have been enrolled in each level.

An independent, external, and multidisciplinary Data Safety Monitoring Committee (DSMC) composed of 3 to 5 members will be established and include at least 1 clinician knowledgeable in the field of the trial and at least 1 statistician. The DSMC will operate according to a prespecified charter and make recommendations on study conduct related to patient safety. The DSMC will review the progress of the study and perform reviews of safety data and provide recommendation to whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.


CCI



9.1.4 Missing Data Imputation and Handling of Values Outside the Limits of Quantitation

Missing values due to a missing sample or failed test will not be imputed. For cytokine assessment only, values reported as below the limit of quantitation (BLQ) at baseline, will be imputed as LLOQ (lower limit of quantitation). If LLOQ is not available, the minimum value across all samples will be used in place of the LLOQ to impute the values reported as BLQ. This imputation approach with LLOQ is only for baseline cytokine values, and not for post-baseline values.

Values reported as above the limit of quantitation (ALQ) post-baseline, will be imputed as ULOQ (upper limit of quantitation). If ULOQ is not available, the maximum value across all samples will be used in place of the ULOQ to impute the values reported as ALQ. The imputation approach is for post-baseline values only, and not for any baseline cytokine values.

10.0 PHARMACOKINETIC ANALYSIS

10.1 Objectives of the Pharmacokinetic Analysis

In addition to the objectives described in this section, PK data obtained in this study may also be combined with data from other studies to develop population PK models. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of NKTR-255 and to determine measures of individual exposure for NKTR-255. Model predicted exposures may be used for exposure-response analyses of selected efficacy and safety endpoints. Population PK and/or exposure-response analyses will be specified in a separate analysis plan and the results will be reported separately.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10.3.2 Handling of Missing Values, BLQ Values, and Outliers

Missing concentration values will not be imputed. When summarizing concentrations, zero values will be excluded from the calculation of geometric means and CV% geometric mean, however, they will be included for all other summary statistics and the number of non-zero concentrations will be reported. Missing values for any PK parameters will not be imputed and will be handled as missing.

When calculating PK parameters, all Cycle 1 pre-dose concentrations that are below the limit of quantification (BLQ) will be set to 0; all other concentrations that are BLQ will be set to missing. Predose concentration for Cycle 2 and onward will be duplicated as D22 (504 hr, trough) for the previous cycle and predose on Day 1 for the scheduled cycle for the calculation of PK parameters. Concentration value of BLQ will be treated as missing for D22 (504 hr) of previous cycle and as 0 for the predose on Day 1 for the scheduled cycle.


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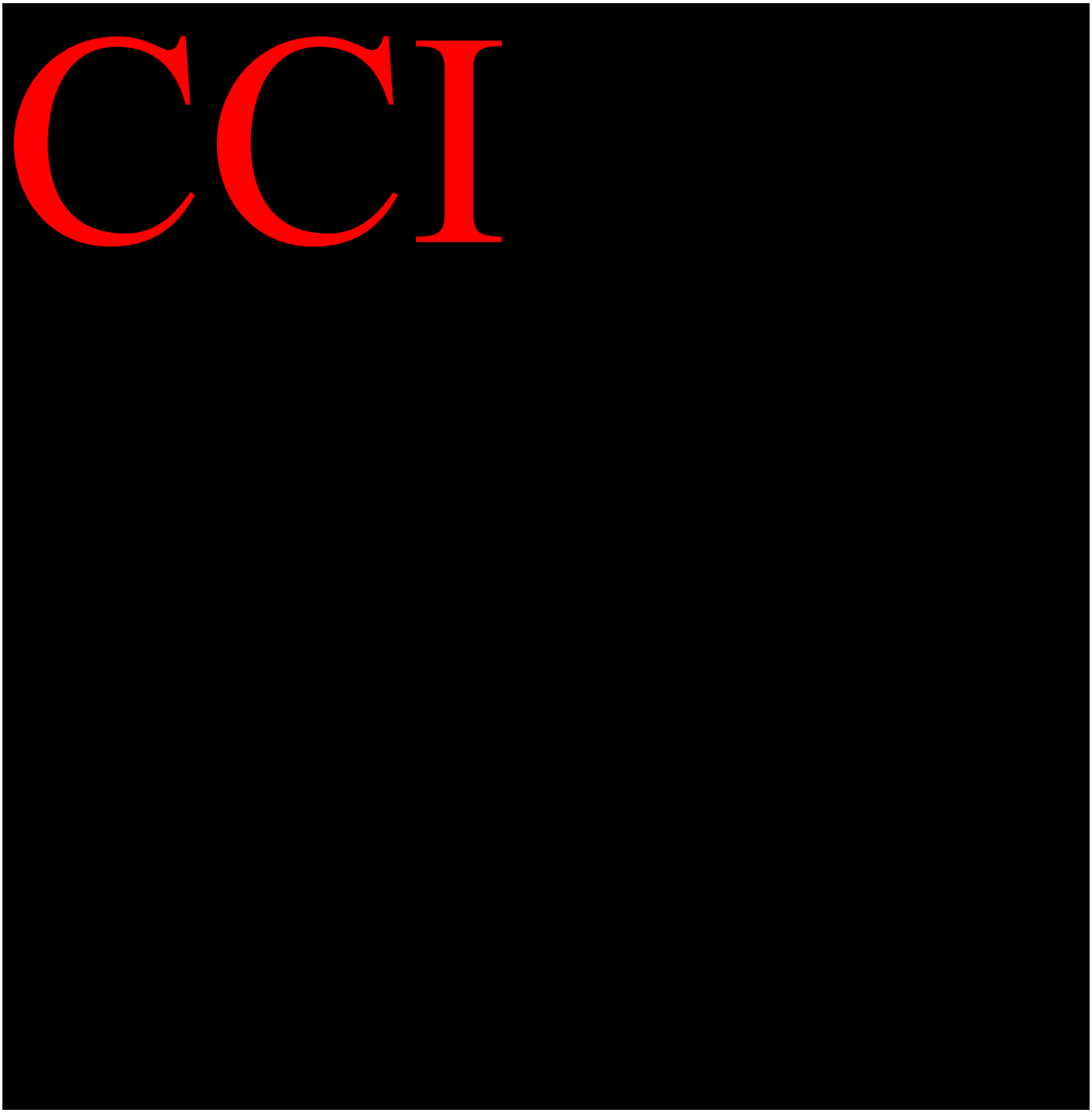
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12.0 CHANGES FROM PROTOCOL

Below are changes of this plan from Nektar Therapeutics Protocol 19-255-03 "A Phase 1b/2, open-label, multi-center, dose escalation and dose expansion study of NKTR-255 in combination with cetuximab as a salvage regimen for solid tumors", protocol amendment 2.0 dated 08 October 2021.

- All analyses methods related to expansion phase of the study are removed as only Phase 1b patients were enrolled
- PFS analysis is based on safety population
- CCI [redacted]
- Updated definition for TEAE period
- Updated definition for Response-evaluable population

13.0 REFERENCES

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