Statistical Analysis Plan

Nektar Therapeutics

Protocol 15-214-01

A Phase 1/2, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-214 in Subjects with Locally Advanced or Metastatic Solid Tumor Malignancies

Protocol Version: **Amendment 4.0 (24 October 2016)**

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Version: **Version 1.0**

Version Date: **02-February-2018**

[redacted]

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List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase (serum glutamic pyruvic transaminase)
AST/SGOT	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
ATC	anatomical therapeutic class
BMI	body mass index
BOI	best overall response
BSA	body surface area
C1D1	Cycle 1/Day 1
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DCB	duration of clinical benefit
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GGT	gamma-glutamy1 transferase
HR	heart rate
irAE	immune-related adverse event
irRC	immune-related response criteria
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MCH	mean corpuscular hemoglobin
MCMC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDSCs	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MTR	median time to response
NCI	National Cancer Institute
NE	not evaluable
NK	natural killer cell
NKTR	Nektar Therapeutics
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease

PE	physical examination
PFS	progression free survival
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PR	partial response
PT	preferred term
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fredericia's formula
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RTF	rich text format
SAE	serious adverse event
SBP	systolic blood pressure
SD	stable disease
SOC	system organ class
T4	free thyroxine
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating cell
TTR	time to response
WBC	white blood cell
WHODDE	World Health Organization Drug Dictionary Enhanced

1 INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical methods to be implemented during the analyses of data collected within the scope of Nektar Therapeutics Protocol 15-214-01 [A Phase 1/2, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-214 in Subjects with Locally Advanced or Metastatic Solid Tumor Malignancies] dated 24 October 2016. The purpose of this SAP is to provide details on the analyses. Any deviations from the SAP will be documented in the clinical study report (CSR).

Details for pharmacokinetic (PK) methods, parameter calculations, and analyses will be included in a separate pharmacokinetic analysis plan (PKAP) prepared by Nektar Clinical Pharmacology. Nektar Clinical Pharmacology will also identify the subjects who are eligible for inclusion in the PK analysis population.

2 STUDY OBJECTIVES

Primary Objectives:

- To evaluate the safety and tolerability, and define the maximum tolerated dose (MTD) of NKTR-214.
- To evaluate the efficacy of NKTR-214 by assessing the objective response rate (ORR) at the MTD or the dose below the MTD.

Secondary Objectives:

- To evaluate the efficacy of NKTR-214 by assessing best overall response (BOR), [redacted] duration of response (DOR), clinical benefit rate (CBR), time to response (TTR), [redacted]
- To characterize the pharmacokinetic (PK) profile of NKTR-214 and relevant metabolites.
- To assess the immunogenicity of NKTR-214.

Exploratory Objectives:

- To assess the immunologic effect of NKTR-214 in tumor tissue on tumor-infiltrating lymphocytes (TIL).
- To assess the immunologic effects of NKTR-214 in blood, including effects on cytokines, natural killer (NK) cells, T-cells, and other serum proteins and immune modulators.

3 STUDY DESIGN AND PLAN

This is a Phase 1/2, open-label, multicenter, dose escalation and dose expansion study of NKTR-214 in subjects with histologically confirmed locally advanced or metastatic malignancies who have measurable disease. The study will consist of a dose escalation phase and a dose expansion phase.

The 3+3 design will be used as a guide to determine the MTD in the dose escalation phase. Additional eligible subjects may be enrolled into the cohort for which the first three subjects are under dose-limiting toxicity (DLT) observation. However, the dose escalation decision will be made when the first 3 subjects in the cohort have completed their DLT observation period. During

the dose escalation period, subjects who are withdrawn from the study during the DLT observation period due to reasons other than toxicity will be replaced. All drug related AEs, including events beyond the DLT observation period, will be taken into account to determine the MTD.

Once the MTD has been reached, lower dose and different dose schedules may be assessed.

4 DETERMINATION OF SAMPLE SIZE

In the dose escalation phase, cohorts of at least 3 subjects will be treated at each dose level and additional subjects may be added to each dose cohort based on the dose assignment action (escalate to a higher dose, stay at the same dose, or de-escalate to a lower dose) or Sponsor determination of the need for additional data to further evaluate the benefit/risk profile. It is estimated that approximately 50 subjects will be enrolled during the dose escalation phase.

Dose expansion will enroll approximately 50 subjects with RCC.

5 GENERAL ANALYSIS CONSIDERATIONS AND DEFINITIONS

The statistical analyses will be reported using summary tables, figures, and data listings. Unless otherwise specified, data collected during the dose escalation phase will be presented by dose cohort and overall. Data collected during the dose expansion phase will be presented by tumor type and overall.

Summary statistics for continuous variables will include the mean, standard deviation, median, minimum, and maximum. The mean 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 presented as frequency counts and percentages. 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 that dose cohort within the population of interest unless otherwise noted.

Time-to-event variables will be analyzed using the Kaplan-Meier method. The number and percentage of subjects with events or censored will be presented. The Kaplan-Meier estimates for quartiles (i.e., 25%, median, and 75%) and the 95% confidence interval for the median will be presented. All time to event variables will be plotted using the Kaplan-Meier method.

All data, including data collected from the electronic case report form (eCRF) and derived for statistical analysis, will be listed.

Cycle 1/Day 1 (C1D1) is defined as the first day of study treatment administration. Other study days will be calculated as follows:

- for any date post the date of C1D1:
  Study day = visit date – date of C1D1 + 1

- for any date prior to the date of Cycle 1/Day 1:
  Study day = visit date – date of C1D1

Unless otherwise specified, the baseline is defined as the last non-missing value prior to C1D1.

6 HANDLING OF MISSING DATA

No imputation will be considered for incomplete data except the following:

- In order to classify medications as concomitant or prior medications, the incomplete stop date for any medication will be imputed as follows:
  - If the year is missing, then the stop date will not be imputed;
  - If both day and month are missing but year is not missing, if the year is prior to the year of C1D1, then the stop date will be imputed as 01/July, otherwise if the year is the same as the year of C1D1, then the stop date will be imputed as 01/January;
  - If the day is missing but the month and year are not missing, and the month and year is the same as C1D1, then the stop date will be imputed as the date of C1D1, otherwise if the month and year is prior to C1D1, then the stop date will be imputed as first day of the month.

- In order to determine the time from last systemic therapy to informed consent, the incomplete stop date for the last systemic therapy will be imputed as follows:
  - If the year is missing, then the stop date will not be imputed;
  - If both day and month are missing but year is not missing, if the year is prior to the year of informed consent, then the stop date will be imputed as 01/July, otherwise if the year is the same as the year of informed consent, then the stop date will be imputed as 01/January;
  - If the day is missing but the month and year are not missing, then the stop date will be imputed as first day of the month.

- In order to determine the duration of last systemic therapy, the incomplete start date for the last systemic therapy will be imputed as follows:
  - If the year is missing, then the stop date will not be imputed;
  - If both day and month are missing but year is not missing, if the year is prior to the year of informed consent, then the start date will be imputed as 01/July, otherwise if the year is the same as the year of informed consent, then the stop date will be imputed as 01/January;
  - If the day is missing but the month and year are not missing, then the start date will be imputed as first day of the month.

- In order to determine the time from initial diagnosis of primary cancer to informed consent and time from initial metastasis diagnosis or most recent local recurrence to informed consent, the incomplete date of diagnosis will be imputed as follows:
    - If the year is missing, then the date of diagnosis will not be imputed;
    - If the day is missing but the month and year are not missing, then the date of diagnosis will be imputed as the first day of the month;
    - If both day and month are missing and the year is prior to the year of informed consent, then the date of diagnosis will be imputed as 01/July, otherwise if the year is the same as the year of informed consent, then the date of diagnosis will be imputed as 01/January.

- In order to determine the duration of AEs, an incomplete start date of any AE will be imputed as follows:
    - If both month and year are missing, then they should be queried and the missing start date of the AE will not be imputed;
    - If start day of the AE is missing but month and year are not missing:
        - If the month of occurrence of the AE is after the month of C1D1, then the missing day will be imputed as the first day of the month;
        - If the month of occurrence of the AE is the same as the month of C1D1, then the missing date will be imputed as the same date of C1D1;

- In order to determine the duration of AEs, incomplete stop date of any AEs will be imputed as follows:
    - If the stop date of any AE is missing but the month and year are not missing, then the stop date will be imputed as last day of the month or the date of discontinuation from the study whichever is the earlier;
    - If both stop date and month of any AE are missing but year is present, then the stop date will be imputed as 31/December or the date of discontinuation from the study, whichever is earliest;
    - If the stop date for any AE is completely missing, then the date will be imputed as date of discontinuation from the study.

7 ANALYSIS POPULATIONS

Safety Population: all subjects who receive at least one dose (or partial dose) of study treatment will be included in the analysis of safety.

DLT Population: all subjects who complete at least one cycle of treatment or discontinue from the study treatment due to DLT will be included.

Pharmacokinetic Population: all subjects in the Safety Population who have relatively complete individual analyte concentration-time profiles that allow for the computation of meaningful PK parameter values.

Response Evaluable Population: subjects who met all eligibility criteria, have measurable disease (per Response Evaluation Criteria in Solid Tumors [RECIST) 1.1) at baseline, and also have at least one post-baseline assessment of tumor response.

8 PLANNED ANALYSES

The following summary will be performed based on the safety population unless otherwise specified.

8.1 Subject Disposition

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

All enrolled subjects will be included in the summary table. All disposition data will be provided in a listing.

8.2 Protocol Deviation

Protocol deviations will be classified as important or non-important and grouped into different categories/subcategories by study team prior to data base lock. The number and percentage of subjects in each protocol deviation category/subcategory will be summarized. All protocol deviations will be provided in a listing.

8.3 Demographic and Baseline Characteristics

Demographic variables will include age, gender, ethnicity, and race. Baseline characteristics will include the Eastern Cooperative Oncology Group (ECOG) performance status, height, weight, and calculated body mass index (BMI). All demographic and baseline characteristics will be summarized for the safety population.

Age will be calculated as:

(Date of the informed consent signed – Date of birth) / 365.25.

BMI will be calculated as:

$$\text{BMI}\,(\text{kg/m}^2) = \frac{\text{Weight}\,(\text{kg})}{[\text{Height}\,(\text{m})]^2},$$

All demographic and baseline characteristics data will be provided in a listing.

8.4 Cancer History

The summary for cancer history will include type of primary cancer, stage at initial diagnosis, time since initial diagnosis of primary cancer to date of informed consent, time since diagnosis of metastatic disease or most recent local recurrence to date of informed consent, current status, stage at most recent recurrence. Incomplete date of initial diagnosis of primary cancer and diagnosis of metastatic disease or most recent local recurrence will be imputed using rules specified in Section 6.

All cancer history data will be provided in a listing.

8.5 Medical History

All medical history and surgery procedures prior to study enrollment will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT). Subjects will be counted only once within each SOC and PT.

All medical history data will be provided in a listing.

8.6 Prior Therapy

All prior systemic therapies will be coded by the World Health Organization Drug Dictionary Enhanced (WHODDE) using the Anatomical Therapeutic Chemical (ATC) Classification System level 2 term (therapeutic main group) and PT. If the level 2 term is missing, then the level 1 term (anatomical main group) will be used. The number and percentage of subjects will be summarized by ATC level 2 term and PT. Subjects will be counted only once within each ATC level 2 term and PT.

The type of prior therapies, time since the last prior systemic therapy to date of informed consent, and total number of prior systemic therapies will be summarized. For the last prior therapy, the best response and the duration of the therapy will be summarized by ATC level 2 term and overall. For last systemic therapy with complete missing start date, duration of the therapy will not be calculated. Otherwise, partial start date will be imputed as specified in Section 6.

All prior cancer therapies including systemic therapy, surgery, and radiotherapy will be provided in a listing.

8.7 Prior and Concomitant Medications and Procedures

All medications will be coded by the WHODDE using ATC level 2 term (therapeutic main group) and PT. If the level 2 term is missing, then the level 1 term (anatomical main group) will be used.

Prior medications are defined as medications with stop date prior to the first dose. Concomitant medications are defined as medications with stop date after the date of first dose. Medications with incomplete stop date will be imputed by rules specified in Section 6. The number and percentage of subjects who have concomitant medications will be summarized by ATC level 2 term and PT. Subjects will be counted only once under each ATC level 2 term and PT.

All procedures performed prior and during the study will be coded by MedDRA using SOC and PT. Only procedures performed after the date of first dose will be summarized. The number and percentage of subjects who have procedures performed after the date of first dose will be summarized by SOC and PT. Subjects are counted once in each SOC and PT.

All prior and concomitant medications and procedures will be provided in a listing.

8.8 Study Exposure

The number and percentage of subjects will be provided by number of infusions. For each cohort, the total number of infusions, total cumulative dose (mg), duration of exposure (months), and relative dose intensity will be summarized. The total cumulative dose is calculated as the sum of

actual dose within each study cycle. The duration of exposure is calculated as the time between the date of first dose to the date of last dose plus 14 or 21 days depending on NKTR dosing frequency or end of treatment date, whichever is earlier. The relative dose intensity is calculated as the actual dose intensity divided by the planned dose intensity. The actual dose intensity is calculated as the total cumulative dose divided by weight at baseline and duration of treatment.

Treatment exposure will be summarized for the safety and PK population.

All treatment exposure data will be listed by subject.

9 EFFICACY ANALYSIS

Efficacy analysis will include best overall response (BOR), objective response rate (ORR), clinical benefit rate (CBR), duration of response (DOR), time to response (TTR), [redacted]

All tumor response and time to event data will be listed by subject.

9.1 Best Overall Response

All lesions, including lymph nodes, will be categorized as target or non-target lesions at baseline and evaluated at each post-baseline tumor assessment to determine the overall response as one of the following: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluated (NE) based on RECIST 1.1 (E.A. Eisenhauer et al. 2009). The best overall response is determined based on the overall response from each post-baseline tumor assessment in the following order: CR, PR, SD, PD, and NE. For CR and PR, changes in tumor measurements must be confirmed by a repeat assessment at least 4 weeks after the time when criteria for CR or PR are first met. The number and percentage of subjects in each best overall response category will be summarized based on response evaluable population.

9.2 Objective Response Rate and Clinical Benefit Rate

ORR is defined as the proportion of subjects who have confirmed CR or PR as their best overall response. CBR is defined as the proportion of subjects who have CR, PR or SD as their best overall response. The number and percentage of subjects who achieve objective response or clinical benefit will be summarized based on response evaluable population. The 95% exact confidence interval using Clopper-Pearson method will be calculated for ORR and CBR. The maximum percentage decrease from baseline in sum of the longest diameter of all target lesions will be plotted for each subject. In addition, BOR and ORR will also be summarized based on all subjects treated.

The immune-related response criteria (irRC) (J.D. Wolchok 2009) may be applied to re-evaluate BOR, ORR, and CBR. The number and percentage of subjects in each category per irRC will be summarized similarly.

All lesion measurements and tumor response assessments will be provided in a listing.

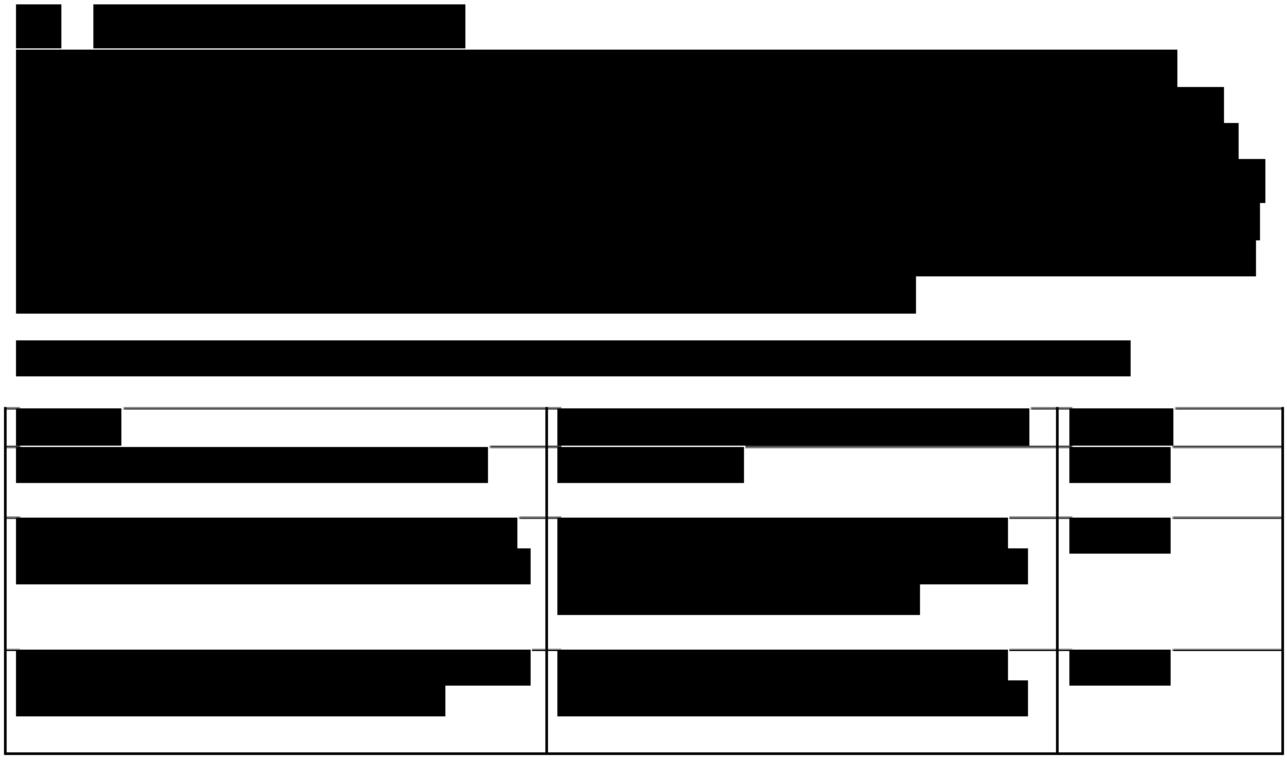
9.3 Time to Response

Time to response (TTR) is only defined for subjects whose best overall response are CR or PR. Time to response is defined as the time from the date of first dose to the date when CR or PR is observed, whichever is earlier. TTR will be listed but not summarized unless there is a sufficient number of subjects who achieve ORR. In such case, TTR will be summarized using descriptive statistics. TTR will also be summarized similarly based on the irRC.

9.4 Duration of Response and Clinical Benefit

Duration of response (DOR) is only defined for subjects whose best overall response is CR or PR. The duration of response is the time between the first CR or PR, whichever is earlier, to progressive disease or death, whichever is earlier. DOR is subject to the censoring rules as given in Table 1. DOR will be listed but not summarized unless there is a sufficient number of subjects who achieve ORR. In such case, DOR will be summarized using the Kaplan-Meier method with number and percentage of subjects who have events or censored, the quartiles (25%, median, and 75%) and 95% confidence interval for the median.

Duration of clinical benefit (DCB) is only defined for subjects whose best overall response are CR, PR, or SD. The duration of clinical benefit is the time between the first CR, PR, or SD whichever is earlier, to progressive disease or death, whichever is earlier. DCB is subject to the censoring rules as given in Table 1. DCB will be listed but not summarized unless there is a sufficient number of subjects who achieve ORR. In such case, DCB will be summarized using the Kaplan-Meier method with number and percentage of subjects who have events or censored, the quartiles (25%, median, and 75%) and 95% confidence interval for the median.



[redacted]

[redacted]

10 SAFETY ANALYSES

All safety analyses will be based on the safety population unless otherwise specified.

10.1 Dose Limiting Toxicity

A dose-limiting toxicity (DLT) is defined as a grade 3 or higher related or possibly related AE occurring within the first cycle of dosing except:

- Grade 3/4 transient lymphopenia < 14 days in duration,
- tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor,
- a transient, reversible ≤ grade 3 infusion AE,
- non-clinically significant laboratory abnormalities, or
- fatigue lasting less than 72 hours

Delayed DLTs are AEs that meet the definition of DLT events and occur after Cycle 1. DLTs and delayed DLTs will be summarized separately for each dose cohort. All DLTs and delayed DLTs will be listed by subject.

10.2 Adverse Events

A treatment emergent adverse event (TEAE) is:

- an AE that was not present prior to treatment and occurred after the first dose of NKTR-214 including partial dose or
- a pre-existing condition that was present before first dose of NKTR-214 and worsened after the first dose of NKTR-214 or
- an AE that was present at treatment initiation, but resolved and then reappeared while the subject was on treatment (regardless of intensity of the AE when the treatment was initiated)

In addition, an AE will be considered to be a TEAE if its status cannot be fully determined due to incomplete data. All AEs will be coded by MedDRA using SOC and PT. Only TEAEs will be summarized in the table. All AEs including non-TEAEs will be listed by subject.

An AE is considered to be related to NKTR-214 if the relationship to study treatment is assessed by investigators as possibly related or related. An AE with missing or unknown relationship will be considered to be a related AE.

For each NKTR-214 related TEAE, the duration of TEAEs will be summarized by SOC and PT. The duration of the NKTR-214 related TEAEs will be calculated as:

Duration of AE = AE stop date – AE start date + 1.

For subjects who have the same NKTR-214 related TEAE multiple times, the duration will be the average of each individual duration. An incomplete start and end date for a NKTR-214 related TEAE will be imputed as specified in Section 6. The duration of AEs will be summarized by SOC and PT.

A TEAE is considered to be a TEAE leading to death if the severity grade is 5 or the outcome is fatal. A TEAE is considered to be a TEAE leading to NKTR-214 discontinuation if the action taken to NKTR-214 is drug withdrawn. A TEAE is considered to be a TEAE leading to NKTR-214 delay, reduction, or interruption if the action taken to NKTR-214 is dose delayed, dose reduced, or dose interruption.

In each summary table, the total number of events and the number and percentage of subjects who have at least one event will be reported. For TEAE summaries by SOC and/or PT, a subject is counted only once within each summary level. For TEAE summary by CTCAE grade, a subject is counted only once using the highest grade.

The following summaries will be provided for AEs:

- TEAEs by SOC and PT,
- TEAEs by PT,
- TEAEs by severity grade, SOC, and PT,
- TEAEs by severity grade, SOC, and PT in cycle 1,
- NKTR-214 related TEAEs SOC and PT,
- NKTR-214 related TEAEs by PT,
- NKTR-214 related TEAEs by severity grade, SOC, and PT,
- Grade≥3 TEAEs by SOC and PT,
- NKTR-214 Related Grade≥3 TEAEs by SOC and PT,

- Serious adverse event (SAEs) by SOC and PT,
- NKTR-214 Related SAEs by SOC and PT,
- TEAEs leading to NKTR-214 delay, interruption, or reduction by SOC and PT,
- TEAEs leading to NKTR-214 discontinuation by SOC and PT,
- TEAEs leading to death by SOC and PT,

Selected AEs of special interest will be grouped by pooled PTs, which are provided in Appendix 16.2. The number and percentage of subjects for each AEs of special interest will be presented.

10.3 Clinical Laboratory Evaluation

Hematology analytes include hemoglobin, hematocrit, red blood cell (RBC), platelet, white blood cell (WBC) and differentials (neutrophils, lymphocytes, monocytes, basophils, and eosinophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry analytes include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, creatinine, calculated creatinine clearance, calcium, glucose, total protein, total bilirubin, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, lactate dehydrogenase, and uric acid.

Coagulation analytes include partial thromboplastin time and prothrombin time.

Descriptive statistics will be provided for baseline, each post-baseline and change from baseline at each post-baseline assessment. A shift table comparing the CTCAE grade at baseline to each post-baseline assessment will be provided for analyte with CTCAE grades. In addition, a shift table comparing the CTCAE grade at baseline to the worst post-baseline assessment will be provided.

Additional laboratory values including creatinine kinase, thyroid stimulating hormone, free thyroxine (T4), lipase, amylase, and HLA typing will be summarized by descriptive statistics at baseline and each post-baseline assessment.

Urinalysis analytes include specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes, esterase, and blood. For subjects with positive protein and white blood cell or blood during urinalysis, microscopic examination will be performed and include RBCs, WBCs, epithelial cells, bacteria, crystals, and casts.

All laboratory data will be listed by subject.

10.4 Vital Signs

Vital signs include weight, heart rate (HR), respiratory rate, temperature, supine systolic blood pressure (SBP), supine diastolic blood pressure (DBP) and oxygen saturation. Descriptive statistics will be provided for each vital sign at baseline, post-baseline, and for change from baseline at each post-baseline assessment.

All vital sign data will be listed by subject.

10.5 Electrocardiogram

Electrocardiogram (ECG) assessments include PR, RR, QRS, QT, correct QT interval using Fredericia's formula (QTcF), corrected QT interval using Bazett's formula (QTcB), and HR. Each analyte will be collected in triplicate at every baseline and post-baseline ECG assessment. Descriptive statistics will be provided for the mean of the triplicate at baseline, post-baseline and change from baseline at each post-baseline assessment.

The number and percentage of subjects in each of the following categories based on QTcB and QTcF will be provided:

- QTc interval ≥ 450 ms,
- QTc interval ≥ 480 ms,
- QTc interval ≥ 500 ms,
- QTc interval change from baseline ≥ 30 ms,
- QTc interval change from baseline ≥ 60 ms.

In addition, the interpretation of ECGs will be categorized as normal or abnormal at each assessment time point. Shift tables will be provided to summarize ECG interpretation change from baseline at each post-baseline assessment.

Echocardiogram includes stress test (normal and abnormal) and left ventricular ejection fraction (LVEF). Descriptive statistics will be provided for LVEF at baseline, post-baseline and for change from baseline at each post-baseline assessment. The number and percentage of subjects who performed a stress test at baseline and at each post-baseline assessment time point will be provided.

11 IMMUNOGENICITY

Validated assays will be used to determine the anti-drug antibodies to NKTR-214. The number and percentage of subjects who have detectable anti-NKTR-214 antibodies will be summarized for subjects in the safety population who provide at least 1 post-treatment sample.

All immunogenicity data will be listed by subject.

12 EXPLORATORY ANALYSES

TBD

13 PHARMACOKINETICS

Pharmacokinetic data collected on the case report forms will be presented in data listings. Details for pharmacokinetic analyses will be provided in a separate analysis plan.

14 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

No changes from the protocol specified analyses are planned.

15 REFERENCES

Eisenhauer E.A., et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, 45 (2):228-47.

Wolchok, J. D., et al. (2009). Guidelines for evaluation for immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*, 15 (23): 7412-20.

16 APPENDICES

16.1 Evaluation of Overall Response using RECIST 1.1

Overall response first time point	Overall response subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD.
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD.
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE.
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD.
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE.
NE	NE	NE

Abbreviations CR, complete response; PR, partial response; SD, stable disease, PD; progressive disease; NE, inevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Source: Eisenhauer, 2009

16.2 Preferred Terms for searching AEs of Special Interest in Safety Analysis

AEs of Special Interest	PTs (MedDRA V20.1)
Rash	erythema
	rash erythematous
	rash maculo-papular
	rash papular
	rash pruritic
	rash pustular
	rash vesicular
	rash generalised
	rash macular
Flu like symptoms	influenza like illness
	pyrexia
	chills
	influenza
Hypotention	hypotension
	blood pressure decreased
Infusion related reaction	infusion related reaction
	hypersensitvity
Pruritus	pruritus
	pruritus generalised
	eye pruritus
	pruritus allergic
Fatigue	asthenia
	fatigue
	decreased activity
	lethargy
	malaise
Angioedema	angioedema
	face oedema
	eye oedema
	eye swelling
	lip oedema
	lip swelling
	mouth swelling
	oedema mouth
	periorbital oedema
	swelling face
	swollen tongue
	tongue oedema
	urticaria

Table continues

AEs of Special Interest	PTs (MedDRA V20.1)
Syncope	syncope
	presyncope
Hepatic Function Abnormal	alanine aminotransferase increased
	aspartate aminotransferase increased
	hepatic enzyme increased
	hepatitis
	hepatitis acute
	liver disorder
	liver function test abnormal
	transaminases increased
	autoimmune hepatitis
Hypothyroidism/Thyroiditis	autoimmune hypothyroidism
	hypothyroidism
	thyroid stimulating hormone deficiency
	autoimmune thyroiditis
	blood thyroid stimulating hormone decreased
	blood thyroid stimulating hormone abnormal
	blood thyroid stimulating hormone increased
	thyroiditis
Hyperthyroidism	hyperthyroidism
Pneumonitis	acute respiratory distress syndrome
	acute respiratory failure
	interstitial lung disease
	lung infiltration
	pneumonitis
	acute interstitial pneumonitis
	acute lung injury
Pancreatitis/Pancreatic enzyme elevation	pancreatitis
	pancreatitis acute
	amylase abnormal
	amylase increased
	lipase abnormal
	lipase increased
	pancreatic enzymes abnormal
	pancreatic enzymes increased
Vitiligo	skin hypopigmentation
	vitiligo