Statistical Analysis Plan

Nektar Therapeutics

Protocol 16-214-05

A PHASE 1/2, OPEN-LABEL, MULTICENTER STUDY TO INVESTIGATE THE SAFETY AND PRELIMINARY EFFICACY OF COMBINED BEMPEGALDESLEUKIN (NKTR-214) AND PEMBROLIZUMAB WITH OR WITHOUT CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

Protocol Version: **Amendment 7.0 (23 December 2020)**

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Abbreviation or Term	Definition
ADA	anti-drug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BOR	best overall response
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HR	heart rate
ICH	International Council for Harmonisation
IL-2	interleukin-2
irAE	immune-related Adverse Events
ICE	ischemic cerebrovascular events
Kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
Min	minute(s)
Mg	milligram
mL	milliliter
MTD	maximum tolerated dose
N1	sample size at stage 1
N2	sample size at stage 2
NCI	National Cancer Institute
NE	inevaluable
NKTR-214	bempegaldesleukin (International Nonproprietary Name)
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease

PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
q3w	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TPS	Tumor Proportion Score
TTR	time to response

1 INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical methods to be implemented for the analyses of data collected within the scope of Nektar Therapeutics Protocol 16-214-05 (A Phase 1/2, Open-label, Multicenter Study to Investigate the Safety and Preliminary Efficacy of Combined Bempegaldesleukin [NKTR-214] and Pembrolizumab with or without Chemotherapy in Patients with Locally Advanced or Metastatic Solid Tumors) dated 23 December 2020. 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).

This Phase 1/2 study is conducted in accordance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

On 14 April 2022, Nektar Therapeutics and Bristol-Myers Squibb jointly decided to end the global clinical development program for bempegaldesleukin. This study and all other ongoing studies in this program will be discontinued.

2 STUDY OBJECTIVES

This section shows the planned primary, secondary, and exploratory objectives from the study protocol. However, due to the closure of the bempegaldesleukin program, analyses and parameter calculations specified in the Protocol for pharmacokinetic (PK), immunogenicity, biomarker (except PD-L1), clinical laboratory, vital signs, physical examination, electrocardiogram (ECG), concomitant medications, clinical benefit rate at 18 weeks (CBR18), clinical benefit rate at 27 weeks (CBR27) are no longer planned to be conducted. Other analyses no longer planned to be performed are other safety observations for NKTR-214, prior medications, prior therapy, medical history, and important protocol deviations. Analyses to address the exploratory objectives also will not be performed.

2.1 Primary Objectives: Dose Optimization or Dose Expansion Cohorts

The primary objectives in the dose optimization cohorts are:

- To evaluate the safety and tolerability of NKTR-214 in combination with pembrolizumab.
- To define the MTD/RP2D and optimal dosing schedule of NKTR-214 in combination with pembrolizumab.

The primary objective in all the dose expansion cohorts is:

- To determine the ORR per blinded independent central review (BICR) by RECIST 1.1 of NKTR-214 plus pembrolizumab with or without systemic chemotherapy in patients with untreated metastatic NSCLC.

2.2 Secondary Objectives: Dose Optimization and/or Dose Expansion Cohorts

The secondary objectives in the dose optimization and/or dose expansion cohorts are:

- To evaluate safety and tolerability of NKTR-214 plus pembrolizumab with or without systemic chemotherapy in patients with untreated NSCLC (dose expansion only).
- To assess the preliminary efficacy (per BICR) of NKTR-214 plus pembrolizumab with or without systemic chemotherapy:
  - Objective response rate (ORR) by RECIST 1.1 (dose optimization only)
  - Duration of response (DOR) by RECIST 1.1
  - Clinical benefit rate (CBR) by RECIST 1.1
  - Time to response (TTR) by RECIST 1.1
  - Progression-free survival (PFS) by RECIST 1.1
  - Overall survival (OS)
- To assess the association between efficacy measures and PD-L1 expression in tumors.

[redacted]

3 STUDY ENDPOINTS

This section shows the planned primary, secondary, [redacted] endpoints from the study protocol. However, due to the closure of the bempegaldesleukin program, analyses and parameter calculations specified in the Protocol for PK, immunogenicity, biomarker (except PD-L1), clinical laboratory, vital signs, physical examination, electrocardiogram, concomitant medications, CBR18, and CBR27 are no longer planned to be conducted. Other analyses no longer planned to be performed are other safety observations for NKTR-214, prior medications, prior therapy, medical history, and important protocol deviations. [redacted]

3.1 Primary Endpoints

Objective	Endpoint	Cohort
• To evaluate the safety and tolerability of NKTR-214 in combination with pembrolizumab. • To define the MTD/RP2D and optimal dosing schedule of NKTR-214 in combination with pembrolizumab.	• Incidence of dose limiting toxicity (DLT) • Incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, Drug-related TEAEs, Grade 3 and above TEAEs, fatal TEAEs and TEAEs leading to treatment discontinuations, immune-related adverse events (irAEs), and ischemic cerebrovascular events (ICE)	Dose Optimization
• To determine the ORR per blinded independent central review (BICR) by RECIST 1.1 of NKTR-214 plus pembrolizumab with or without systemic chemotherapy in patients with untreated metastatic NSCLC.	• Objective response rate (ORR)	Dose Expansion*

* Efficacy endpoints for cohort 4 and 5 will be per Investigator's assessments due to early termination of the study and incompleteness of BICR data for these cohorts; Efficacy endpoints for other dose expansion cohorts and dose optimization cohorts will be per BICR.

3.2 Secondary Endpoints

Objective	Endpoint	Cohort
• To evaluate safety and tolerability of NKTR-214 plus pembrolizumab with or without systemic chemotherapy in patients with untreated NSCLC (dose expansion only).	• Incidence of TEAEs, serious TEAEs, Drug-related TEAEs, Grade 3 and above TEAEs, Fatal TEAEs and TEAEs leading to treatment discontinuations, immune-related adverse events (irAEs), and ischemic cerebrovascular events (ICE)	Dose Expansion
• To assess the preliminary	• ORR	Dose Optimization

efficacy (per BICR) of NKTR-214 plus pembrolizumab with or without systemic chemotherapy • To assess the association between efficacy measures and PD-L1 expression in tumors.	• Duration of response (DOR) • Clinical benefit rate (CBR) • Time to response (TTR) • Progression-free survival (PFS) • Overall survival (OS)	
	• Duration of response (DOR) • Clinical benefit rate (CBR) • Time to response (TTR) • Progression-free survival (PFS) • Overall survival (OS)	Dose Expansion*

* Efficacy endpoints for cohort 4 and 5 will be per Investigator's assessments due to early termination of the study and incompleteness of BICR data for these cohorts; Efficacy endpoints for other dose expansion cohorts and dose optimization cohorts will be per BICR.

[redacted]

[redacted]

4 STUDY DESIGN AND PLAN

This is a Phase 1/2, open-label, multicenter, study of NKTR-214 in combination with pembrolizumab with or without systemic chemotherapy in patients with metastatic solid tumors.

The dose optimization cohorts (Cohorts 1a and 1b) will include first- and second-line (1L and 2L) melanoma, non-small cell lung cancer (NSCLC), urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), and hepatocellular carcinoma (HCC). The dose optimization Cohort 1a will include patients enrolled in the 3 + 3 dose optimization cohort and the dose optimization Cohort 1b will include patients enrolled in the step-up dose optimization cohort.

The dose expansion cohorts (Cohorts 2, 3, 4, and 5) will include first-line NSCLC patients, first-line nonsquamous NSCSC patients, and first-line squamous cell lung cancer patients.

The original protocol and amendments (up to and including Amendment 4), evaluated atezolizumab in combination with NKTR-214 (0.006 mg/kg) for treatment of second-line NSCLC and first- and second- line urothelial carcinoma and pembrolizumab in combination with NKTR-214 (0.006 mg/kg) for treatment of first-line metastatic melanoma and first- and second-line NSCLC. Patients in the pembrolizumab first-line NSCLC cohort will continue on study in the dose expansion cohort of Amendment 5.0 or subsequent versions; however, the atezolizumab second-line NSCLC and first- or second-line urothelial carcinoma cohorts and the pembrolizumab first-line melanoma cohort have been closed to further enrollment. Patients on study who were enrolled in these cohorts under prior amendments will continue treatment as described in Amendment 5.0 and subsequent versions. Patients will be followed for efficacy and safety until the patient is lost to follow-up, withdraws consent, or patient death.

Analysis of subjects enrolled before Amendment 5.0 will be separate from the analysis of subjects enrolled under Amendment 5.0 and subsequent versions.

The study is divided into a Screening period, Treatment period, End of Treatment (EOT) and Long-Term Follow-up period. The treatment cycles are every 21 days (3 weeks).

5 DETERMINATION OF SAMPLE SIZE

In Amendment 7.0 and subsequent versions, approximately 40 patients may be enrolled in Dose Optimization Cohorts 1a and 1b, approximately 58 response-evaluable patients may be enrolled in Dose Expansion Cohorts 2 and 3, and approximately 63 response-evaluable patients may be enrolled in Dose Expansion Cohorts 4 and 5. Patients who are not response-evaluable or who have insufficient biopsy material for PD-L1 assessment may be replaced. Up to 100 patients may be enrolled in each cohort to reach the number of responsible-evaluable patients. The sample size for Cohorts 1a and 1b is based on expected cohort number for dose optimization. The sample sizes for Cohorts 2, 3, 4, and 5 are based on the Fleming 2-stage design framework and historical comparators.

For the dose optimization cohorts of NKTR-214 in combination with pembrolizumab for patients with locally advanced metastatic solid tumors, cohorts of at least 3 patients will be treated at each dose level. Additional patients will be added to each dose cohort based on the schema and rules outlined in Section 5.3 in the protocol or Sponsor determination of the need for additional data to further evaluate the benefit/risk profile. It is estimated that approximately 40 patients will be enrolled into the dose optimization cohorts.

For efficacy assessment of the dose expansion cohorts (first-line NSCLC patients), the sample size is strictly based on efficacy, specifically based on the target ORR relative to historic response rate per each PD-L1 categorization.

The Fleming 2-stage design (Fleming 1982) framework will be used as a guide for the 1L NSCLC Expansion Cohorts 2, 3, 4, and 5. The total sample size for each 1L NSCLC expansion cohort (TPS <1%, TPS 1% to 49%, and TPS ≥50%) will be calculated based on a one-sided Type 1 error of 10% and a power of 90%. The 2-stage design provides an option to stop early for futility as well as allowing an expansion of enrollment if a strong antitumor activity signal is observed. However, the final decision will be based on the totality of overall treatment effect for multiple study endpoints and their associations with the tumor response rate. Enrollment may continue into Stage 2 while the planned number of patients for Stage 1 are followed for response-evaluable tumor assessments. There will be no stopping of enrollment to a tumor cohort for efficacy, although early planning for the next stage of clinical development may be initiated.

Cohorts 2 and 3

Approximately 58 response-evaluable first-line NSCLC patients may be enrolled in Cohort 2 (and in Cohort 3 if opened), including: Cohort 2.1/3.1: minimum 20 PD-L1 < 1%, Cohort 2.2/3.2: minimum 18 PD- L1 1% to 49%, and Cohort 2.3/3.3: minimum 20 PD-L1 ≥ 50%. Patients who are not response-evaluable and patients whose PD-L1 status is unable to be confirmed by central testing will be replaced (Table 1).

Table 1 - True (Target) and Historic Objective Response Rate for First-line NSCLC by PD-L1 Categorization (Cohorts 2 and 3)

		Objective Response Rate (ORR) (%)[a]		**Sample Size (Minimum Sample Size)[b]**			**Futility**		**Efficacy**	
Cohort	**Indication**	Historical	Target	N1	N2	Total	S1	S2	T1	T2
2.1/3.1	NSCLC 1L (PD-L1 <1 %)[c]	8	30	12	8	20	0	≤ 3	≥ 3	≥ 4
2.2/3.2	NSCLC 1L (PD-L1 1% to 49 %)[c]	14	40	8	10	18	0	≤ 4	≥ 4	≥ 5
2.3/3.3	NSCLC 1L (PD-L1 ≥ 50%)	25	55	11	9	20	≤ 3	≤ 7	≥ 6	≥ 8

Abbreviations: N1 = sample size at Stage 1; N2 = sample size at Stage 2; NSCLC = non-small cell lung cancer; ORR = objective response rate; PD-L1 = programmed cell death ligand 1; S1 = futility boundary at Stage 1; S2 = futility boundary at Stage 2; T1 = efficacy boundary at Stage 1; T2 = efficacy boundary at Stage 2.

a. Reference for historical ORR assumption: Carbone 2017; Garon 2015.

b. Sample size for each expansion cohort is calculated using a normal approximation to provide a reasonable false-positive rate (FPR < 10%) and false-negative rate (FNR < 10%). This is the minimum-required sample size needed to achieve targeted number of response-evaluable patients.

c. For France only: patients in first-line NSCLC dose expansion Cohorts 2.1/3.1 and 2.2/3.2 with PD-L1 status < 50% are excluded.

Cohorts 4 and 5

Based on safety and efficacy data from Cohorts 2 and 3, a decision may be made to open Cohorts 4 (1L nonsquamous NSCLC) and 5 (1L squamous NSCLC). Up to 63 response evaluable patients may be enrolled in each of Cohorts 4 and 5, using the Fleming 2-stage design framework. Patients who are not response-evaluable or who have insufficient biopsy material for PD-L1 assessment may be replaced.

Approximately 61 response-evaluable first-line NSCLC patients may be enrolled in Cohort 4, including: Cohort 4.1: 21 PD-L1 <1%, Cohort 4.2: 21 PD- L1 1% to 49%, and Cohort 4.3: 19 PD-L1 ≥50% (Table 2).

Approximately 63 response-evaluable first-line NSCLC patients may be enrolled in Cohort 5, including: Cohort 5.1: 21 PD-L1 <1%, Cohort 5.2: 21 PD- L1 1% to 49%, and Cohort 5.3: 21 PD-L1 ⩾50% (Table 2).

Table 2 - True (Target) and Historic Objective Response Rate for First-line NSCLC by PD-L1 Categorization (Cohorts 4 and 5)

		Objective Response Rate (ORR) (%)[a]		Sample Size (Minimum Sample Size)[b]			Futility		Efficacy	
Cohort	**Indication**	Historical	Target	N1	N2	Total	S1	S2	T1	T2
4.1	NSCLC 1L (PD-L1 <1 %)[c]	32%	60%	13	8	21	<= 4	<= 9	>= 8	>= 10
4.2	NSCLC 1L (PD-L1 1% to 49 %)[c]	49%	77%	9	12	21	<= 4	<= 13	>= 8	>= 14
4.3	NSCLC 1L (PD-L1 ≥ 50%)	62%	87%	9	10	19	<= 5	<= 14	>= 9	>= 15
5.1	NSCLC 1L (PD-L1 <1 %)[c]	63%	88%	11	10	21	<= 7	<= 16	>= 10	>= 17
5.2	NSCLC 1L (PD-L1 1% to 49 %)[c]	50%	77%	9	12	21	<= 4	<= 13	>= 8	>= 14

		Objective Response Rate (ORR) (%)[a]		Sample Size (Minimum Sample Size)[b]			Futility		Efficacy	
Cohort	**Indication**	Historical	Target	N1	N2	Total	S1	S2	T1	T2
4.1	NSCLC 1L (PD-L1 <1 %)[c]	32%	60%	13	8	21	<= 4	<= 9	>= 8	>= 10
5.3	NSCLC 1L (PD-L1 ≥ 50%)	60%	85%	14	7	21	<= 9	<= 15	>= 12	>= 16

Abbreviations: N1 = sample size at Stage 1; N2 = sample size at Stage 2; NSCLC = non-small cell lung cancer; ORR = objective response rate; PD-L1 = programmed cell death ligand 1; S1 = futility boundary at Stage 1; S2 = futility boundary at Stage 2; T1 = efficacy boundary at Stage 1; T2 = efficacy boundary at Stage 2.

a. Reference for historical ORR assumption: Gadgeel 2020 (Keynote-189), Paz-Ares 2020 (Keynote-407).

b. Sample size for each expansion cohort is calculated using a normal approximation to provide a reasonable false-positive rate (FPR < 10%) and false-negative rate (FNR < 10%). This is the minimum-required sample size needed to achieve targeted number of response-evaluable patients.

c. For France only: patients in first-line NSCLC dose expansion Cohorts 4.1/5.1 and 4.2/5.2 with PD-L1 status < 50% are excluded.

6 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 PD-L1 level 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 (CI) for the median will be presented. Progression free survival and overall survival 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.

Baseline and Study Days

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 C1D1:

  Study day = visit date – date of C1D1

Unless otherwise specified, the baseline is defined as the last non-missing value on or prior to C1D1 date and time (or, if C1D1 time is not available, the last non-missing value on or prior to C1D1 date). For vital signs the C1D1 pre-dose value will be used as baseline value unless otherwise specified.

For post-baseline value,

- The record closest to the day for visit will be chosen.
- If there are 2 records equidistant from the target visit day, the later record will be chosen
- If there is more than 1 record on the selected day, the latest will be taken, unless otherwise specified. If multiple measurements exist with the same collection date, then the last observation by sequence is used.

7 HANDLING OF MISSING DATA

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

- For prior systemic cancer therapies and medical history of cancer, the study day corresponding to the start and stop date of the regimen will be calculated when calculating duration of the therapy/history and relevant time to the initiation of the study, etc. For partially missing start dates, missing day of the month will be imputed as the first day of the month and missing month will be imputed as January. For partially missing stop dates, missing day of the month will be imputed as the last day of the month and missing month will be imputed as December and at least 1 day after the start date. No imputation will be done if the year is missing.

- For prior radiotherapy and surgery, the relevant time to the initiation of the study, etc. will be calculated using the calculated study day corresponding to the date of radiotherapy or date of procedure for surgery. The imputation rules described for prior systemic cancer therapy will be applied to prior radiotherapy and surgery.

- For time from initial diagnosis to enrollment and time from diagnosis of metastatic disease to enrollment, partial dates for initial diagnosis and diagnosis of metastatic disease will be imputed as follows:
  - No imputation will be done if the year is missing.
  - If the year is before enrollment date then missing days will be imputed as the first day of the month and missing months will be imputed as July.
  - If the year is the current year of enrollment date then missing days will be imputed as the first day of the month and missing months will be imputed as January.

- For duration of AEs, partial dates for **start** of AE will be imputed as follows:
  - Missing day, month, and year are not allowed and should be queried. In case of non-resolution of missing month and/or year, no imputation will be performed.
  - Start day of AE is missing and the year is same as Cycle 1 Day 1 (C1D1)
    - If the reported month of occurrence of AE is after the month of C1D1 dose then missing day will be imputed as the first day of the month of occurrence of AE.
    - If the reported month of occurrence of AE is the month of C1D1 dose then the missing day will be imputed as the same day as C1D1.
  - Start day of AE is missing and the year is after the year of C1D1
    - Missing day will be imputed as the first day of the month of occurrence of AE.

- For duration of AEs, partial dates for **stop** of AE will be imputed as follows:
  - Missing day, month, and year are not allowed and should be queried. In case of non-resolution of missing year, no imputation will be performed.
  - If only the day is missing, the last day of that month, the date of discontinuation from the study, or the date of death, whichever is earlier, will be used as the stop date.
  - If month and day are missing, then December 31st, the date of discontinuation from the study, or the date of death, whichever is earlier, will be used as the stop date.

- For determination of prior medication, any medication with a start date prior to C1D1 will be classified as prior medication regardless of when the stop date is. Missing or partial dates will be handled as follows:
  - If missing day and/or month of the start date, the medication will be classified as prior unless the month and/or year of the start date is after C1D1.

- For determination of concomitant medication, the following will be classified as concomitant medication:
  - Any medication with a start date prior to or on C1D1 and continued after C1D1.
  - Any medication with a start date after C1D1, and prior to or on 90 days after the last dose date.

- Missing or partial dates for concomitant medication will be handled as follows:
  - If missing day and/or month of the start date, the medication will be excluded from concomitant if the month and/or year of the start date is after the last dose date + 90 days.
  - If missing day and/or month of the stop date, the medication will be excluded from concomitant if the month and/or year of the stop date is prior to C1D1.
  - A medication with completely missing start and stop dates will be classified as concomitant.

8 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 the DLT observation period or discontinue from the study treatment due to DLT will be included.

Response Evaluable Population: subjects who have received at least 1 dose (or partial dose) of study drug, have measurable disease (per RECIST 1.1) at baseline, and have at least one post-baseline assessment of tumor response.

9 PLANNED ANALYSES

All statistical summaries and analyses will be separated by dose level (3+3 cohort) and dose sequence (step-up cohort) in the dose optimization cohorts and by PD-L1 status in the dose expansion cohorts, unless specified otherwise.

Subjects enrolled prior to Amendment 5.0 will be analyzed by drug combination (atezolizumab and pembrolizumab) unless otherwise specified.

9.1 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 reasons 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.

9.2 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.

BMI will be calculated as:

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

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

9.3 Cancer History

The summary of 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, type of prior therapies, and time since the last prior systemic therapy to date of informed consent. Incomplete date of initial diagnosis of primary cancer, diagnosis of metastatic disease or most recent local recurrence, and last systemic therapy will be imputed using rules specified in Section 7.

All cancer history data will be provided in a listing.

9.4 Concomitant Medications

Due to the early termination of this study as a consequence of the closure of the bempegaldesleukin clinical program, the planned analyses in the protocol will not be performed.

9.5 Study Exposure

For each cohort, the total number of infusions, total cumulative dose (mg), duration of exposure, 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. The relative dose intensity is calculated as the actual dose intensity divided by the planned dose intensity.

Body Surface Area (BSA) will be calculated as (Mosteller 1987):

BSA (m^2) = squared root of ((weight in kg * height in cm)/3600)

Actual dose intensity for Carboplatin at cycle will be calculated using the Calvert formula:

Actual Total Dose / (GFR+25),

where the GFR will be calculated by the Cockcroft-Gault equation (Cockcroft 1976):

GFR (male; mL/min) = (140 – age) × (weight in kg) / (72 × serum creatinine (mg/dL))
GFR (female; mL/min) = 0.85 × GFR (male)

For NKTR-214, the following parameters will be calculated:

- Actual dose intensity (mg/kg/week): [Cumulative dose (mg/kg) / (Exposure duration in days + 20 days)] × 7
- Expected dose intensity (mg/kg/week) = (Planned Dose at C1D1 / (3 weeks) = 0.002 mg/kg/week
- Relative dose intensity (%): (Actual dose intensity / Expected dose intensity) × 100

For pembrolizumab, the following parameters will be calculated:

- Actual dose intensity (mg/week): [Cumulative dose (mg) / (Exposure duration in days + 20 days)] × 7
- Expected dose intensity (mg/week) = (200 mg) / (3 weeks) = 67 mg/kg/week
- Relative dose intensity (%): (Actual dose intensity / Expected dose intensity) × 100

For cisplatin, the following parameters will be calculated:

- Actual dose intensity (mg/m2/week): [Cumulative dose (mg/m^2) / (Exposure duration in days + 20 days)] × 7
- Expected dose intensity (mg/m2) = (75 mg/m^2) / (3 weeks) = 25 mg/m^2/week
- Relative dose intensity (%): (Actual dose intensity / Expected dose intensity) × 100

For carboplatin, the following parameters will be calculated:

- Actual dose intensity (mg/(ml/min)/week): [Cumulative dose (mg/(ml/min)) / (Exposure duration in days + 20 days)] × 7
- Expected dose intensity (mg/(ml/min)/week) = (5 mg/(ml/min)) / (3 weeks) = 1.67 mg/(ml/min)/week
- Relative dose intensity (%): (Actual dose intensity / Expected dose intensity) × 100

For pemetrexed, the following parameters will be calculated:

- Actual dose intensity (mg/m^2/week): [Cumulative dose (mg/m^2) / (Exposure duration in days + 20 days)] × 7
- Expected dose intensity (mg/m^2/week) = (500 mg/m^2) / (3 weeks) = 167 mg/m^2/week
- Relative dose intensity (%): (Actual dose intensity / Expected dose intensity) × 100

For paclitaxel, the following parameters will be calculated:

- Actual dose intensity (mg/m^2/week): [Cumulative dose (mg/m^2) / (Exposure duration in days + 20 days)] × 7
- Expected dose intensity (mg/m^2/week) = (200 mg/m^2) / (3 weeks) = 67 mg/m^2/week
- Relative dose intensity (%): (Actual dose intensity / Expected dose intensity) × 100

For nab-paclitaxel, the following parameters will be calculated:

- Actual dose intensity (mg/m^2/week): [Cumulative dose (mg/m^2) / (Exposure duration in days + 20 days)] × 7
- Expected dose intensity (mg/m^2/week) = (100 mg/m^2) / (3 weeks) = 33 mg/m^2/week
- Relative dose intensity (%): (Actual dose intensity / Expected dose intensity) × 100

Treatment exposure will be summarized for the safety population.

All treatment exposure data will be listed by subject.

9.6 Efficacy Analysis

All tumor response and progression outcomes will be evaluated using RECIST 1.1 by Investigator assessment for Cohort 4 and 5 due to incompleteness of BICR data, and by BICR for other cohorts.

- Best overall response (BOR) using RECIST 1.1
- Objective response rate (ORR) using RECIST 1.1
- Clinical benefit rate (CBR) using RECIST 1.1
- Time to response (TTR) using RECIST 1.1
- Duration of response (DOR) using RECIST 1.1
- Progression-free survival (PFS) using RECIST 1.1
- Overall survival (OS)

Time to event variables (PFS and OS) will be plotted. All tumor response and time to event data will be listed by subject.

Subjects enrolled prior to Amendment 5.0 will not be summarized.

9.6.1 Tumor Response (BOR, ORR, and CBR)

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. The BOR is determined based on the overall response from each post-baseline tumor assessment per RECIST 1.1 (Eisenhauer 2009; also see Section 14.1) in the following order: CR, PR, SD, PD, and NE.

Tumor assessments after the first PD, new systemic anti-cancer therapy, irradiation or resection (i.e., surgical procedures or radiotherapy on target lesions) will not contribute to the BOR assessment. 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. For the confirmation of CR or PR, there could be one (1) tumor assessment with overall response NE

between the first and the subsequent CR or PR. Additionally for the confirmation of PR, there could be one (1) SD between the first PR to the subsequent PR. For SD, changes in tumor measurements must last for at least 56 days.

The number and percentage of subjects in each BOR category will be summarized based on the response evaluable population.

The ORR is defined as the proportion of subjects who have CR or PR as their BOR. The CBR is defined as the proportion of subjects who have CR, PR or SD (at least 8 weeks or longer from C1D1) as their BOR. The number and percentage of subjects who achieve objective response or clinical benefit will be summarized based on the response evaluable population. The 95% CI will be calculated using the exact binomial method.

9.6.2 Time to Response

For patients who achieved CR or PR, TTR is defined as the time from the date of first dose to the date of first response (i.e., CR or PR). TTR will be summarized for the response evaluable population using descriptive statistics.

9.6.3 Duration of Response

For patients who achieved CR or PR, DOR is defined as the time between the first response (i.e., CR or PR) to progressive disease per RECIST 1.1 or death due to any cause, whichever is earlier. DOR is subject to the PFS censoring rules as given in Table 3.

DOR will be listed but not summarized unless there is a sufficient number of subjects who achieve ORR.

9.6.4 Progression Free Survival

PFS is defined as the time between the date of first dose to the date of progressive disease per RECIST 1.1 or death due to any cause, whichever is earlier. PFS is subject to censoring rules as given in Table 3. PFS will be summarized for the safety population using the Kaplan-Meier method. The summary will include number and percentage of subjects who have event or censored, the quartiles (25%, median, and 75%), and 95% CI for the median. In addition, the proportion of subjects who are alive at 6 months and 12 months and the 95% CI will be calculated using the Kaplan-Meier method.

Table 3 - Censoring Rules for Progression Free Survival

Situation	Date of Disease Progression or Censoring	Outcome
No baseline assessments for tumor response	Date of first dose	Censored
No post-baseline assessments for tumor response and no death	Date of first dose	Censored

Not known to have progressed or died according to data in the database as of data-cut-off	Date of last evaluable tumor assessment showing no evidence of disease progression	Censored
Subsequent anti-cancer therapy / irradiation or resection started without death or progression per RECIST v1.1 reported prior to or on the same day observing PD or death	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Documented progression per RECIST v1.1 and no new anti-cancer therapy started before	Date of the first documented progression per RECIST v1.1	Progressed
Death without progression per RECIST v1.1 and no new anti-cancer therapy started before	Date of death	Progressed

9.6.5 Overall Survival

The overall survival (OS) is defined as the time between the date of first dose to the date of death from any cause. Subjects who do not have date of death will be censored on the last date known to be alive. OS will be summarized for the safety population using the Kaplan-Meier method. The summary will include number and percentage of subjects who have event or censored, the quartiles (25%, median, and 75%), and 95% CI for the median. In addition, the proportion of subjects who are alive at 6 months and 12 months and the 95% CI will be calculated using the Kaplan-Meier method.

9.7 Safety Analyses

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

9.7.1 Dose Limiting Toxicity

DLTs will be evaluated within the DLT evaluation window as specified in the protocol. Delayed DLTs are AEs that are defined in the protocol that occur after the DLT evaluation window. DLTs and delayed DLTs will be summarized separately by SOC and PT. All DLTs and delayed DLTs will be listed by patient.

9.7.2 Adverse Events

A treatment-emergent adverse event (TEAE) is:

- Any AE that happens on or after treatment initiation
- AE that was present at time of treatment initiation but worsened after treatment initiation
- AE that was present and resolved prior to treatment and reappeared after treatment initiation.

Incomplete start and end date for TEAEs will be imputed. Any AE will be considered as a TEAE if its status cannot be fully determined because of incomplete data. The treatment-emergent period will be defined as the period of time on or after the date/time of the first dose of study drug

administration (on or after the date of the first dose of study drug administration, if time is not available) until the earlier date of the two dates:

- Date of initiation of new antineoplastic regimen
- 30 days (90 days for SAEs) after the date of the last dose of all study drug

Only TEAEs will be summarized in the table. All AEs including non-TEAEs will be listed by subject.

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. AE severity will be determined based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade (version 5.0).

A TEAE is considered as related to treatment if it is related or possible related to NKTR-214, pembrolizumab, atezolizumab or chemotherapy. A TEAE is considered as leading to treatment discontinuation if it is leading to discontinuation of NKTR-214, pembrolizumab, atezolizumab or chemotherapy.

In each summary table, 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 TEAEs (atezolizumab-related summaries will similarly be included where applicable for subjects enrolled under Amendment 4 or earlier):

- Overall summary of TEAEs,
- TEAEs by SOC and PT,
- Serious TEAEs by SOC and PT,
- Drug-related TEAEs by SOC and PT,
- Fatal TEAEs by SOC and PT,
- Grade 3 and above TEAEs by SOC and PT,
- TEAEs leading to study drug discontinuation by SOC and PT.

9.7.3 Adverse Events of Special Interest for Pembrolizumab

Immune-related Adverse Events (irAEs)

All potential non-endocrine or endocrine irAEs along with concomitant medication information will be reviewed by Clinical Development, and Clinical Development will manually determine and provide a final list of irAEs for the irAE summaries.

For irAE analysis, treatment-emergent period based on period of time from the date/time of the first dose of study drug until the earlier date of the following two dates will be used:

- Date of initiation of new antineoplastic regimen
- 90 days after the date of the last dose of all study drug.

IrAEs will be summarized by safety population. The number and percentage of subjects who have at least one event will be reported.

All irAEs will be listed by subject.

9.7.4 Adverse Events of Special Interest for Bempegaldesleukin

The AESI for bempegaldesleukin consist of ischemic cerebrovascular events (ICE). The ICE will be identified using the SMQ: Ischaemic central nervous system vascular conditions (SMQ) - Narrow Scope.

All AESIs will be listed by subject.

9.7.5 Clinical Laboratory, Vital Signs, Physical Examination and Electrocardiogram

Due to the early termination of this study as a consequence of the closure of the bempegaldesleukin clinical program, the planned analyses in the protocol will not be performed.

10 IMMUNOGENICITY

Due to the early termination of this study as a consequence of the closure of the bempegaldesleukin clinical program, the planned analyses in the protocol will not be performed.

[redacted]

12 PHARMACOKINETICS

Due to the early termination of this study as a consequence of the closure of the bempegaldesleukin clinical program, the planned PK analyses in the protocol will not be performed.

13 REFERENCES

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14 APPENDICES

14.1 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, unevaluable.
[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