Nektar Therapeutics

STATISTICAL ANALYSIS PLAN

A Phase 2 Single-Arm Study of Bempegaldesleukin (NKTR-214) in Combination with Nivolumab in Cisplatin Ineligible, Locally Advanced or Metastatic Urothelial Cancer Patients

Protocol Number: 18-214-10/ CA045-012, Amendment 5.0

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PREPARED BY:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AC	active cytokine/s
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATCL	anatomical, therapeutic chemical level classification
AUC	area under the curve
BICR	blinded independent central review
BLQ	below the limit of quantification data
BOR	best overall response
C1D1	Cycle 1 Day 1
CBR	clinical benefit rate
CI	confidence interval
CLS	capillary leak syndro
CLT	clinical trial lead
CPS	combined positive score
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CS	Clinically Significant
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
DOR	duration of response
DVT	deep vein thrombosis
ECLA	electrochemiluminescence assay
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ELISA	enzyme-linked immunosorbent assays
EORTC QLQ-C30	European Organization for the Research and Treatment of
EOS	eosinophil
EQ-5D-3L	3-level version of the EuroQol Group's EQ-5D
GemCarbo	gemcitabine/carboplatin
GCP	Good Clinical Practice
GP5	Functional Assessment of Chronic Illness Therapy (FACIT)

Abbreviation	Definition
HGB	hemoglobin
HoTN	hypotension
HR	hazard ratio
HRQoL	health-related quality of life
ICE	ischemic cerebrovascular events
IDMC	Independent data monitoring committee
IFNγ	interferon gamma
IHC	immunohistochemistry
IL-2	interleukin-2. *For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule.*
IMAEs	immune-mediated adverse events
irAEs	Immune-related adverse events
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
LYMPH	lymphocyte count
MedDRA	Medical Dictionary for Regulatory Activities
mUC	metastatic urothelial carcinoma
NE	not evaluable
NKTR-214-AC	active bempegaldesleukin-related molecules
NKTR-214-RC	bempegaldesleukin-related molecules
OirAESI	other immune-related adverse event of special interest
ORR	objective response rate
OS	overall survival
OSO	other safety observations
PD	progressive disease, *or* Pharmacodynamics *in PK analysis*
PD-L1	programmed cell death ligand 1
PE	physical examination
PEG	polyethylene glycol
PFS	progression-free survival
PK	pharmacokinetic(s)
PLAT	platelet count
PR	partial response
PT	preferred term
q3w	every 3 weeks
QoL	quality of life

Abbreviation	Definition
RECIST	response evaluation criteria in solid tumors
RC	related cytokine/s
RS	Raw Score
SAE	serious adverse event
SD	stable disease
SMQ	Standardized MedDRA Query
SOC	system organ class
TEAE	Treatment-Emergent adverse event
TIA	transient ischemic attack
TIL	tumor infiltrating lymphocytes
TNM	tumor node metastasis
Total-PEG	total polyethylene glycol
TTR	Time to response
ULN	upper limit of normal
WBC	white blood count
WHO-DDE	World Health Organization Drug Dictionary Enhanced

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 safety specimens, and samples for biomarkers, immunogenicity, pharmacokinetics (PK), and pharmacodynamics(PD). An interactive response technology (IRT) service provider will manage the enrolment system, study drug and inventory management. Data for this trial will be entered into an Electronic Data Capture (EDC) system, using a Medidata Rave platform. Response and progression will be determined by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1; see Response Criteria Using RECIST 1.1 in Section 8.4 of the clinical study protocol).

2.0 INTRODUCTION

This document describes the planned statistical analyses of the efficacy, safety, pharmacokinetic/pharmacodynmanic (PK/PD), biomarker and immunogenicity data captured according to Nektar Therapeutics Protocol 18-214-10 "A Phase 2, single-arm study of bempegaldesleukin (NKTR-214) in combination with nivolumab in cisplatin ineligible, locally advanced or metastatic urothelial cancer patients." version amendment 5.0 dated 27 May 2021.

This Phase 2 study is conducted in accordance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements. In the event of a synoptic CSR resulting from a negative evaluation of the efficacy and safety readouts of the study, only key efficacy and safety analyses described in this analysis plan will be performed to support the synoptic CSR.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is:

- To evaluate the anti-tumor activity of bempegaldesleukin in combination with nivolumab by assessing the ORR by RECIST 1.1 per blinded independent central review (BICR) in patients whose tumors have low PD-L1 expression.

3.2 Secondary Objectives

The secondary objectives are:

- To evaluate the effect of bempegaldesleukin in combination with nivolumab by assessing the ORR by RECIST 1.1 per BICR in all treated patients
- To evaluate the effect of bempegaldesleukin in combination with nivolumab by assessing DOR by RECIST 1.1 per BICR in all treated patients and patients whose tumors have low PD-L1 expression

- To evaluate the effect of bempegaldesleukin in combination with nivolumab by assessing the ORR and DOR by RECIST 1.1 per Investigator assessment in all treated patients and patients whose tumors have low PD-L1 expression
- To evaluate the safety and tolerability of bempegaldesleukin in combination with nivolumab.

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4.0 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

- ORR in patients with low PD-L1 expression treated with bempegaldesleukin/nivolumab, defined as the percentage of patients with a confirmed objective response of complete response (CR) or partial response (PR) per RECIST 1.1 by BICR in patients with low PD-L1 tumor expression.

4.2 Secondary Efficacy Endpoints

- ORR in patients treated with bempegaldesleukin/nivolumab, by RECIST 1.1 by BICR in all treated patients
- DOR in patients treated with bempegaldesleukin/nivolumab, by RECIST 1.1 per BICR in patients with low PD-L1 tumor expression and in all treated patients
- ORR and DOR in patients treated with bempegaldesleukin/nivolumab by RECIST 1.1 per investigator in all treated pateitns and in patients with low PD-L1 tumor expression.

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5.0 OVERALL STUDY DESIGN AND PLAN

5.1 Study Design

This is a single-arm, Phase 2 study evaluating the safety and efficacy of bempegaldesleukin in combination with nivolumab in cisplatin ineligible patients with locally advanced or metastatic UC. Patients will be able to enroll regardless of their baseline PD-L1 expression, however, study enrollment will stop once at least 110 patients whose tumors have low PD-L1 expression have been enrolled and have received at least 1 dose of bempegaldesleukin/nivolumab. For the primary analysis, PD-L1 status will be based on the PD-L1 immunohistochemistry (IHC) 28-8 PharmDx assay reporting the combined positive score (CPS). Exploratory efficacy analysis will be performed using PD-L1 status based on the PD-L1 IHC 22C3 pharmDx assay. A patient is considered to have low PD-L1 expression if CPS < 10 and high PD-L1 expression is CPS ≥ 10. The primary analysis will be performed approximately 18 months after the last patient has been enrolled into the study.

The study has a Screening period, Treatment period, and Long-Term Follow-up period. Patients will receive the following treatment (bempegaldesleukin/nivolumab arm):

- Bempegaldesleukin/nivolumab: bempegaldesleukin 0.006 mg/kg intravenous (IV) and nivolumab 360 mg IV every 3 weeks (q3w) (on Day 1 of each 3-week cycle).

Though the study is mainly focused on this treatment, another treatment option for patients randomized under Protocol Amendment 2 (gemcitabine/carboplatin [GemCarbo] arm) is as follows:

- GemCarbo: Gemcitabine 1000 mg/m^2 IV (on Day 1 and 8 of each 3-week cycle) and carboplatin IV, target area under the curve (AUC) 4.5 mg/mL/min q3w (on Day 1 of each 3-week cycle).

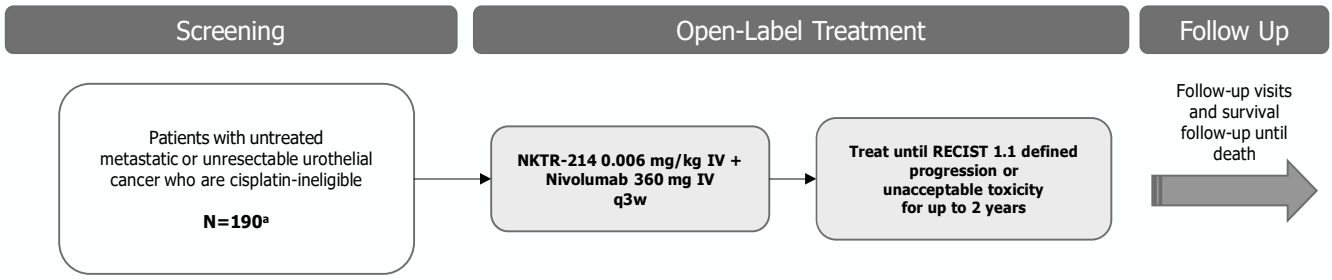
The patients enrolled prior to Protocol Amendment 3 were randomized 2:1 to the bempegaldes-leukin/nivolumab arm or GemCarbo arm. The trial was amended (Amendments 3 -5) to a single arm study with all patients enrolled in the bempegaldesleukin/nivolumab arm.

Since there were very few patients treated with GemCarbo, limited analyses will be performed for the GemCarbo treated patients. Therefore, the rest of this document focuses on analyses planned for patients allocated to the bempegaldesleukin/nivolumab arm unless otherwise specified.

The study was monitored by an IDMC that conducted the initial review of safety and other relevant data after the first 20 patients received at least 2 cycles (6 weeks) of study treatment. Patients will continue to be enrolled while the IDMC is conducting this review.

Following the initial IDMC review on safety and other relevant data, a Sponsor Executive Committee (SEC) will conduct formal safety reviews. The SEC consists of Nektar's Chief Medical Officer, Head of Data Science and Systems, and Head of Regulatory Affairs, none of whom are directly involved in study conduct. The SEC will formally review ongoing safety on

Phase 2 Study of NKTR-214+Nivo: CURRENT
Amendment 3.0: single-arm



IV = intravenous; q3w = every 3 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1

NOTE: Data from the first 20 patients who received at least 2 cycles of bempegaldesleukin and nivolumab will be included in the initial safety review conducted by the Independent Data Monitoring Committee (IDMC).

a. Study aims to enroll at least 110 patients whose tumors have low PD-L1 expression (based on PD-L1 IHC 22C3 PharmDx assay) and who have received at least one dose of bempegaldesleukin/nivolumab; a maximum of approximately 190 patients will be enrolled in the study, including 2 patients who received GemCarbo under Amendment 2.0 of the protocol.

5.2 Study Medications

Patients will be treated until disease progression by RECIST 1.1 or loss of clinical benefit per investigator assessment, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the patient decision to discontinue treatment or withdraw consent, the patient is lost to follow up, Sponsor decides to terminate the study, or for a maximum of 2 years of treatment on bempegaldesleukin/nivolumab.

In case of bempegaldesleukin toxicity requiring treatment delay or discontinuation, the patient may continue treatment with nivolumab if deemed in the best interest of the patient by the Investigator. In case of nivolumab toxicity requiring treatment delay or discontinuation, the patient may continue treatment with bempegaldesleukin if deemed in the best interest of the patient by the Investigator.

Treatment may continue beyond disease progression in the bempegaldesleukin/nivolumab arm if there is clinical benefit as determined by the Investigator.

5.2.1 Bempegaldesleukin Combined with Nivolumab

Each patient's bempegaldesleukin dose will be determined by the patient's weight in kilograms, which will be determined before the start of each 3-week cycle (± 3 days). If the patient's weight has changed more than 10% from Cycle 1 Day 1 weight, the dose of bempegaldesleukin must be recalculated and subsequent weight measurements should be compared with this new baseline weight to determine if further bempegaldesleukin dose recalculations are necessary. Bempegaldesleukin will be administered IV over 30 (±5) minutes at a dose of 0.006 mg/kg on Day 1 of each 3-week cycle.

Bempegaldesleukin will be administered first before nivolumab. Nivolumab administration should start 30 minutes from the end of bempegaldesleukin administration. Patients should receive nivolumab at a dose of 360 mg as a 30-minute infusion on Day 1 of each 3-week cycle and no less than 18 days from the previous dose.

5.3 Pharmacokinetic, Pharmacodynamic, and Biomarker Study Measurements and Endpoints

Blood samples for the assessment of bempegaldesleukin and nivolumab concentrations will be collected and measured. Tumor tissue and blood samples will be collected and measured for pharmacodynamic and biomarker assessments.

5.3.1 Blood Sampling Times

PK, immunogenicity, and biomarker/pharmacodynamic assessments will be collected from study patients at the sampling times indicated in Table 1. Biomarker/pharmacodynamic analyses will be performed on tumor tissue and blood samples.

Table 1: Pharmacokinetic, Immunogenicity, and Blood Biomarker Sampling Schedule

Study Cycle/Day Cycle = every 3 weeks	Event (Relative to Start of Bempeg Infusion)	Time (Relative to Start of Bempeg Infusion) Hour:Min	Bempeg Blood Samples		Nivo Blood Samples		Biomarker
			PK[e]	IMG	PK	IMG	
Cycle 1 Day 1	Predose[a]	00:00	X	X	X	X	X[f]
	End of infusion[b]	00:30	X				
		04:00[c]	X				
Cycle 1 Day 3		48:00[c]	X				X[g]
Cycle 1 Day 5		96:00[d]	X				X[g]
Cycle 1 Day 8		168:00[d]	X				
Cycle 2 Day 1	Predose[a]	00:00	X	X	X	X	X[f]
Cycle 5 Day 1	Predose[a]	00:00	X	X	X	X	X[f]
Cycle 8 Day 1	Predose[a]	00:00					X[f]
Cycle 11 Day 1	Predose[a]	00:00	X	X	X	X	X[f]
Cycle 17 Day 1	Predose[a]	00:00	X	X	X	X	X[f]
Cycle 25 Day 1	Predose[a]	00:00	X	X	X	X	X[f]
Cycle 33 Day 1	Predose[a]	00:00	X	X	X	X	X[f]
Follow-up 30 Day				X	X	X	
Follow-up 100 Day				X	X	X	

Bempeg = bempegaldesleukin; Nivo = nivolumab; IMG = immunogenicity; PK = pharmacokinetic

a. Predose samples should be collected within 24 hours before the start of any dose infusion.

b. The end of infusion sample should be taken immediately prior to stopping the bempegaldesleukin infusion (preferably within 2 minutes prior to the end of infusion). End of infusion samples may not be collected from the same IV access as drug was administered. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

c. Time window for 4-hour sample is ± 1 hour; time window for 48-hour samples is -1 day (i.e., 24 to 48 hours)

d. Time window for Day 5 and Day 8 sample is ± 1 day

e. The bempegaldesleukin PK blood samples will also be used for assessing cytokines and sCD25.

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5.3.1.1 Tumor Biopsy Times

Tumor biopsies or archival tissues will be collected as described in Table 2.

Table 2: Tumor Biopsy Sample Schedule

Collection Timing	Tumor Biopsy
Screening	X[a]
Cycle 1 Days 14-21[b]	X
Upon progression[b]	X

a. Unstained formalin-fixed paraffin-embedded (FFPE) tumor tissue sections on slides (minimum of 10, preferably 15 to 25) or a FFPE tumor tissue block, collected within 12 months prior to enrollment and without intervening therapy, are acceptable in lieu of a fresh tumor biopsy prior to treatment.

b. Sample collection is optional but highly recommended.

5.3.2 Pharmacokinetic Measurements and Endpoints

For bempegaldesleukin, bempegaldesleukin-related molecules (NKTR-214-RC), active bempegaldesleukin-related molecules (NKTR-214-AC), and total polyethylene glycol (Total-PEG) will be measured. NKTR-214-RC and Total-PEG will be analyzed using fully validated enzyme-linked immunosorbent assays (ELISA). NKTR-214-AC will be analyzed using a qualified ELISA.

Nivolumab will be analyzed using a fully validated ELISA.

The analysis methods described in Section 10.1 will be used to estimate the following cycle 1 PK parameters for NKTR-214-RC, NKTR-214-AC for individual patients based on observed concentration values:

- C_{max}: Maximum plasma concentration following drug administration expressed in units of ng/mL
- T_{max}: Time to reach C_{max} expressed in units of hr.
- AUC_{last}: Area under the plasma analyte concentration-time curve calculated from time 0 to the last measurable concentration

Additional PK parameters such as the followings may also be calculated if noncompartmental analysis requirements are met:

- AUC_{inf}: Area under the plasma analyte concentration-time curve calculated from time 0 to infinity
- CL: Systemic clearance from plasma
- $t_{1/2}$: Half-life: the time required for the concentration of the drug to reach half of its original value
- V_z: Volume of distribution during the terminal elimination phase

5.5 Immunogenicity Measurements and Endpoints

Blood samples for the assessment of anti-drug antibodies (ADA) to bempegaldesleukin and nivolumab will be collected and measured as described in Table 1.

Validated methods to detect anti-nivolumab, anti-bempegaldesleukin, anti-PEG and anti-IL-2 ADA will be used to analyze immunogenicity samples. Immunogenicity sample testing will be done in tiers as per the FDA guidance: Immunogenicity Testing of Therapeutic Protein Products - Developing and Validating Assays for Anti-Drug Antibody Detection. Guidance for Industry (FDA 2019). Samples will be first tested with screening electrochemiluminescence assays (ECLAs). Putative positive samples for anti-nivolumab, anti-bempegaldesleukin or anti-IL-2 ADA will then be analyzed in competition ECLAs to confirm positivity. Confirmed anti-bempegaldesleukin ADA-positive samples will be tested further in a polyethylene glycol (PEG) immuno-competition assay to determine the antibody specificity of the reactivity to the PEG or non-PEG (IL-2, linker) moiety of the bempegaldesleukin. Confirmed positive samples from each assay (anti-nivolumab, anti-bempegaldesleukin and anti-IL-2) will then be tested to obtain a titer. Samples confirmed to be ADA-positive will also be tested for neutralizing activity for IL-2 and nivolumab using validated cell-based assays.

6.0 STATISTICAL CONSIDERATIONS

6.1 General Considerations

Although this is an open label study, masking during the trial will be applied for all aggregated data analysis prior to final database lock as detailed in a separate document (18-214-10 Aggregate Data Handling Plan).

The main focus of this trial is on treated patients in the bempegaldesleukin/nivolumab Arm. Some patients were randomized to the GemCarbo Arm under Protocol Amendment 2, among whom some patients may cross over to the bempegaldesleukin/nivolumab treatment. Only limited analyses will be performed on patients in the GemCarbo Arm.

Summary statistics for continuous variables will include the mean, standard deviation, median, minimum, 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, maximum, and quartiles 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 when 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 patients in the population of interest unless otherwise noted. The 95% exact confidence interval for proportions will be calculated by the Clopper-Pearson method (Clopper and Pearson, 1934) for select binary efficacy endpoints.

Time-to-event variables will be summarized with quartiles and range, and analyzed using the Kaplan-Meier (KM) method. The KM estimates for quartiles and the 95% confidence interval for the median derived based on Greenwood's formula (Greenwood, 1926) for variance derivation will be presented. Select time to event variables will be plotted using the KM method.

Data listings will be created to support each table when needed. Data listings will be presented by patient number.

6.2 Determination of Sample Size

The original protocol planned to enroll approximately 185 patients to receive bempegaldesleukin and nivolumab. Amendment 2.0 added a GemCarbo arm and reduced the overall number of patients planned to approximately 165 (110 to receive bempegaldesleukin/nivolumab, 55 to receive GemCarbo). Amendment 3.0 eliminated the GemCarbo arm after 2 patients had enrolled in this arm, and modified the overall planned number of bempegaldesleukin/nivolumab patients to 175. With Amendment 5.0, enrollment is complete at 2 patients who received GemCarbo and 190 patients who received bempegaldesleukin/nivolumab.

The study will evaluate the totality of the data including DOR, and ORR, and CR rate.

Although this study is enrolling both PD-L1 low and PD-L1 high expressors in an unselected fashion, the sample size is determined by the PD-L1 low population. Review of available urothelial carcinoma-specific PD-L1 data suggests that approximately 70% of patients have PD-L1 low tumors (CPS < 10), while 30% have PD-L1 high tumors using the PD-L1 IHC 22C3 pharmDx assay (pembrolizumab) (CPS ≥ 10) (Vuky, 2018; KEYTRUDA Prescribing Information, 2018; TECENTRIQ Prescribing Information, 2018).

This trial will enroll at least 110 patients who have tumors that are PD-L1 low. The null hypothesis is that the ORR is ≤ 21%. The alterative hypothesis is that the ORR is > 21%. The null hypothesis was based on the Keynote-052 study of 1L pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer; in that study, ORR was 20.3% in patients with PD-L1 CPS < 10 (Vuky, 2018).

Assuming an ORR of 34%, with 110 patients, the study will have 82% power to demonstrate that the lower limit of the 95% two-sided confidence interval (CI) for ORR exceeds 21%, where the CI is calculated by the exact computation method.

6.3 Analysis Populations

Screened patients: All patients who signed study participation informed consent.

Enrolled patients: All patients who are assigned to either the bempegaldesleukin/nivolumab or GemCarbo Arm.

NKTR-214, Nivolumab or GemCarbo Treated Population: All patients who are enrolled in the bempegaldesleukin/nivolumab Arm or the GemCarbo Arm under Protocol Amendment 2, and have received at least one full or partial dose of any study drug. Since there are few patients who received GemCarbo in the study, limited analyses will be performed under this population.

Treated Population: All patients who are enrolled in the bempegaldesleukin/nivolumab Arm and have received at least one full or partial dose of study drug bempegaldesleukin/nivolumab. This is the analysis set for all efficacy and safety analyses, as well as corresponding demographics, baseline disease characteristics, and study drug administration unless otherwise specified.

Treated PD-L1 Low Population: All PD-L1 low patients in the Treated Population. Low PD-L1 expression will be defined as CPS < 10. This is the analysis set for all efficacy and safety analyses in PD-L1 low patients, as well as, corresponding demographics, baseline disease characteristics, and study drug administration.

Treated PD-L1 High Population: All PD-L1 high patients in the Treated Population. High PD-L1 expression will be defined as CPS ≥ 10. This is the analysis set for all efficacy and safety analyses in PD-L1 high patients, as well as corresponding demographics, baseline disease characteristics, and study drug administration.

BICR Measurable Disease Treated Population: All patients in the Treated Population who had the measurable disease per BICR at baseline.

BICR Measurable Disease Treated PD-L1 Low Population: All PD-L1 low patients in the Treated Population who had the measurable disease per BICR at baseline.

BICR Measurable Disease Treated PD-L1 High Population: All PD-L1 high patients in the Treated Population who had the measurable disease per BICR at baseline.

Pharmacokinetics Population: All patients in the Treated Population who have at least one quantifiable concentration value for either NKTR-214-RC, NKTR-214-AC, Total-PEG, or nivolumab.

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Immunogenicity Population: All patients in the Treated Population with at least baseline and one post-baseline ADA assessment.

BICR Efficacy Evaluable Population: All patients in the Treated Population who have measurable disease at baseline and also have at least one post-baseline tumor assessment per BICR.

6.4 Handling of Missing Data

In order to summarize and perform the statistical analyses, missing or incomplete data will be imputed. Missing data will be handled as follows as described in Sections 6.4.1 through 6.4.6.

6.4.1 Prior and Concomitant Medication

For determination of prior medication, any medication with a start date prior to Cycle 1 Day 1 (C1D1) will be classified as prior medication regardless of the stop date. 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 the last study dose + 100 days or (date of initiation of new antineoplastic regimen − 1 day), whichever is earlier.

Any medication with a start date prior to C1D1 and continued after C1D1 will be considered as both prior and concomitant medication.

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 not be considered as concomitant if the month and/or year of the start date is after the last dose date + 100 days or (date of initiation of new antineoplastic regimen − 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 stop dates will be classified as concomitant

In order to calculate the duration of immune-modulating medication for management of drug-related select immune-related AEs (irAEs) or immune-mediated AEs (IMAEs), missing or partial dates for these medications will be handled as follows:

Missing or partial start date:

- If the start date is complete missing, it will not be imputed. Only the number of days that the medication was taken on or after the AE start date will be counted toward the duration of IMM for management of certain AE.
- If only year is provided, impute the start date to January 1st of the year,

- If only day is missing, impute the start date to the first day of the month.

Missing or partial stop date:

- If the stop date is complete missing, impute stop date to last known alive date.
- If only year is provided, impute the stop date to December 31st of the year. If the imputed date is after the last known alive date, then set the stop date to the last known alive date.
- If only day is missing, impute the stop date to the last day of the month. If the imputed date is after the last known alive date, then set the stop date to the last known alive date.

6.4.2 Cancer History and Prior Systemic Cancer Therapy

In order to determine the time from initial diagnosis of primary cancer to C1D1 and time from initial metastasis diagnosis or most recent local recurrence to C1D1, 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 C1D1, then the date of diagnosis will be imputed as 01 July, otherwise if the year is the same as the year of C1D1, then the date of diagnosis will be imputed as 01 January.

6.4.3 Subsequent Anti-Cancer Therapy

For the subsequent anti-cancer therapy, the incomplete start date will be imputed as follows:

- Completely missing start dates will remain missing, with no imputation applied;
- If the day is missing but the month and year are not missing:
    - If the end date of the subsequent anti-cancer therapy is complete:
        - Minimum of (the last day of the month, end date of the subsequent anti-cancer therapy)
    - If the end date of the subsequent anticancer therapy is not complete:
        - the last day of the month.
- If both month and day are missing but year is not missing, then the date will be imputed as
    - If the end date of the subsequent anti-cancer therapy is complete:
        - Maximum of (Minimum of (01 July + partial year, end date of the subsequent anti-cancer therapy), C1D1 + 1)

- If the end date of the subsequent anticancer therapy is not complete:
  - If only the day of the end date of the subsequent anticancer therapy is missing, imputed the end date as the last day of the month, and then impute the start date as Maximum of (Minimum of (01 July + partial year, end date of the subsequent anti-cancer therapy), C1D1 + 1).
  - If both the month and the year of the end date are missing, then impute the end date as the last day of the year, and then impute the start date as as Maximum of (Minimum of (01 July + partial year, end date of the subsequent anti-cancer therapy), C1D1 + 1).

6.4.4 Adverse Events

In order to determine the duration of AEs, incomplete start date of any AE will be imputed as follows:

- Missing day, month, and year should be queried.
- If the start date of AE is completely missing, then the missing date will be imputed as the C1D1 date.
- Start day of AE is missing and the year is same as C1D1
  - If the reported month of occurrence of AE is after the month of C1D1 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 then the missing day will be imputed as the same day as C1D1.
  - If the reported month of AE start date is before the month of C1D1 then the missing day will be imputed as day 15 of the month of AE start date. This event is not a TEAE.
  - If the month of AE start date is missing, missing day will be imputed as the date of 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.
  - If the month of AE start date is missing, missing day will be imputed as 01 January of the year of AE start date.

For duration of AEs, partially missing 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 last known alive date, or the date of death, whichever is earliest, will be used as the stop date
- If month and day are missing, then 31 December, the last known alive date, or the date of death, whichever is earliest, will be used as the stop date.

6.4.5 Death

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date and the maximum will be considered as the death date.
- If both the month and the day are missing, January 1st will be used to replace the missing month/day. The imputed date will be compared to the last known alive date and the maximum will be considered as the death date.
- If the date is completely missing but the reason for death is present, the death date will be imputed as the last known date alive.

6.4.6 Other Imputation

Some laboratory analytes may be reported by range (e.g., gamma-glutamyl transferase [GGT] < 17 U/L) and will be imputed by the boundary (e.g., 17 U/L).

No imputation of other missing data is planned.

6.5 Definitions

- Reference date (Day 1) = first dose date of study medication. If a patient has not been treated, the reference day will be set as missing.
- Study Day = assessment date – reference date + 1 for assessment performed on or after the reference date; assessment date – reference date for assessment performed before the reference date.
- Cycle Day = assessment date - date of the first day of the cycle + 1.
- Baseline: Baseline will be defined as the last non-missing value on or before the date of administration of the first dose of study medication (and time if available) unless it is identifiable by time that the value is after the first dose.
- Last known alive date: Last known alive date will be defined as the latest alive date on or before the data cutoff date, captured from the multiple sources. Note that if there is an event date (either an assessment or death) beyond the data cutoff date, the last known alive date will be the data cutoff date. If a subject died before or on the cutoff date, last known alive date will be set as the death date. Last known alive date will not be imputed, except in the case that the death date is partially missing (see details in Section 6.4).
- Best Overall Response (BOR): the best response recorded from the start of the treatment until first occurrence of disease progression or recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started) or the start of a new anticancer therapy.

- Objective Response Rate (ORR): the percentage of patients with a confirmed objective response of complete response (CR) or partial response (PR) by RECIST 1.1 on or before first progressive disease (PD) and any subsequent anticancer therapy, per BICR and per investigator, respectively. A second observation of response is required at least 4 weeks after the initial response to confirm the first observation.
- Duration of Response (DOR): in patients with confirmed objective response, defined as the number of days from the first objective response per RECIST 1.1, per BICR and per investigator, to the first disease progression or death due to any cause, whichever is earlier. Patients who do not progress or die will be censored on the date of their last evaluable tumor assessment.
- Time to Response (TTR): defined for patients who have a confirmed CR or PR as the date of first dose to the first confirmed CR or PR by RECIST 1.1, per BICR and per investigator.
- Progression-free Survival (PFS), primary analysis definition: time from first dose to the first disease progression per RECIST 1.1 by BICR, or death due to any cause, whichever comes first. Patients who do not experience disease progression or death will be censored on the date of their last evaluable tumor assessment, or their first dose date if they do not have any on-study tumor assessment or if they do not have baseline assessment.
- Overall Survival (OS): time from first dose to death from any cause. Patients who do not have a date of death will be censored at their last known alive dates.
- The clinical benefit rate (CBR): the percentage of patients with a confirmed CR or PR, or stable disease (SD) by RECIST 1.1, per BICR and per investigator, respectively, where SD requires an observation of SD at least 35 days from the first day of study treatment.
- Treatment-Emergent Period and Extended Treatment-Emergent Period:

  For patients on treatment, both the treatment-emergent period and the extended treatment-emergent period will be defined as the period of time on or after the day (and time, if collected and not missing) of the first dose of study treatment.

  For patients off treatment, the treatment-emergent period is defined as the period of time on or after the day (and time, if collected and not missing) of the first dose of study treatment, until:

  - Earlier date of initiation of new anticancer therapy – 1 day and **30** days after the date of the last dose of any study treatment

  The extended treatment-emergent period will be defined as the period of time on or after the day (and time, if collected and not missing) of the first dose of study treatment, until:

  - Earlier date of initiation of new anticancer therapy – 1 day and **100** days after the date of the last dose of any study treatment

Study Drug Exposure

The following parameters will be calculated for each of the study drugs (bempegaldesleukin and nivolumab):

- Exposure duration (days): Date of last dose – date of first dose (C1D1) + 1
- Number of cycles: Total number of complete or partial treatment cycles the patient received
- Total number of infusions: Total number of infusions for which the patient received non-zero dose across all cycles
- Cumulative dose (mg/kg and mg): Total actual dose (mg/kg and mg) the patient received across all cycles, defined as the sum of actual doses (mg/kg and mg) received across all cycles
- Average dose per infusion (mg/kg and mg): Cumulative dose (mg/kg and mg) / Total number of infusions
- Average duration of infusion: Total infusion time / Total number of infusions; where total infusion time = summation of (completion time of infusion – start time of infusion) for all infusions of a patient

For bempegaldesleukin, 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) = (0.006 mg/kg) / (3 weeks) = 0.002 mg/kg/week
- Relative dose intensity (%): (Actual dose intensity/Expected dose intensity) × 100

For nivolumab , 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) = (360 mg) / (3 weeks) = 120 mg/week
- Relative dose intensity (%): (Actual dose intensity / Expected dose intensity) × 100

6.6 Visit Windows

Depending on the analysis, single values may be required for each analysis. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis does not. If there are multiple valid, non-missing records in an analysis, the following selection rules will be used to select a single value as needed:

- For baseline value,
    - In general, the baseline value will be the last, non-missing value on or prior to the date and time (if available) of the first dose, unless otherwise specified. If multiple measurements occur on the same day, the last non-missing value on or prior to date of first dose date will be considered the baseline value. If multiple assessments exist with the same collection date (and same time if collected), then the last observation by sequence is used as baseline.

- For post-baseline value,
    - The record closest to the day for that 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 (and same time if collected), then the last observation by sequence is used.

7.0 STATISTICAL ANALYSIS

7.1 Patient Disposition

A summary of patient disposition will display the number of patients who were enrolled, treated and who comprised the analysis populations. In addition, the number of patients who discontinued study drug and the number of patients who exited the study, both overall and by reason, will be presented. Descriptive statistics for the study treatment duration, which is defined as the time (months) between the last dose of any study treatment and the first dose of any study treatment, will be summarized. Descriptive statistics for time to NKTR-214 discontinuation (mean, median, min, max) will be summarized for the patients who discontinued NKTR-214.

All disposition data will be presented in a data listing.

7.2 Important Protocol Deviations

Important protocol deviations are a subset of the protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

Important protocol deviations are defined as protocol deviations that fall into the following categories:

- Violated key inclusion/exclusion criteria
    - Patient did not have stage IV disease at time of enrollment. Patient does not have a histology/cytology with a dominate urothelial cell component
    - Patient does not have measurable disease per RECIST 1.1 criteria.
    - Patient was previously treated with a systemic therapy for inoperable locally advanced or mUC.
    - Patient relapsed within 12 months of receiving last treatment of perioperative chemotherapy
    - Patient did not meet any of the cisplatin-ineligible criteria
    - Patient received prior palliative radiotherapy within 14 days before C1D1
    - Patient does not meet inclusion/exclusion criteria for lab values (e.g., WBC, ANC, platelet count, hemoglobin, creatine clearance, AST/ALT, bilirubin, etc.)
    - Patient's LVEF was less than 46%
    - Patient has active brain metastases or leptomeningeal metastases
    - Patient had prior active malignancy within the previous 3 years
    - Patient has an active known or suspected autoimmune disease
    - Patient has a condition requiring systemic treatment with either corticosteroids (> 10 mg daily) or other immunosuppressive medications within 14 days of C1D1
    - Patients received prior IL-2 therapy
    - Patient received prior treatment with an immune checkpoint or immune-oncology therapy
    - Patient had an active infection requiring systemic therapy within 14 days prior to C1D1
    - Patient has a history of pulmonary embolism (PE), deep vein thrombosis (DVT), or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event (e.g., internal jugular vein thrombosis) within 3 months prior to enrollment.
    - Patient needing more than 2 anti-hypertensive medications for managing hypertension. Patients with hypertension must be on a stable antihypertensive regimen (defined as no dose adjustments to antihypertensive medications) for the 14 days prior to Cycle 1 Day 1
- Received wrong treatment or significantly incorrect dose
    - Treated differently from protocol-specified regimens.

  - Relative dose intensity >125% for study drug (programmatically derived).
- Received important prohibited medication/therapy during study participation
  - Any antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or investigational agent)
- Missing critical primary/key secondary efficacy assessment
  - The baseline disease assessment is missing in BICR data (programmatically derived)
- Issues that affect patient rights
  - Patient did not sign the informed consent for the study before study procedures being performed
  - Patient developed withdraw criteria during the study but were not withdrawn (manual review)
- Other issues that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a patient's rights, safety, or well-being

Final determination of important protocol deviations will be reviewed by the study team (including Clinical Trial Lead (CTL), the Medical Monitor, and the statistician).

The number and percentage of patients in each important protocol deviations category and sub-category will be summarized for the treated patient population. All protocol deviations will be listed.

Final list of the important protocol deviations and the associated categories will be determined by the study team before the database lock.

The number and percentage of patients in each important protocol deviations category and sub-category will be summarized for the NKTR-214, nivolumab or GemCarbo Treated Population . All protocol deviations will be listed.

7.3 Demographics and Other Baseline Disease Characteristics

The following baseline data will be summarized and listed for the Treated PD-L1 Low Population, Treated Population, and Treated PD-L1 High Population:

- Age
- Age category I (< 65, >= 65)
- Age category II (< 65, >= 65 and < 75, >= 75)
- Age category III (< 65, >= 65 and < 75, >= 75 and < 85, >= 85)
- Gender (Male vs. Female)
- Weight
- Height

- Ethnicity
- Race
- Geographic region (US/Canada, Europe, Rest of World)
- ECOG performance status
- Reason for cisplatin ineligibility
- Baseline PD-L1 by 28-8 assay
- Initial diagnostic classification
- Primary tumor location at diagnosis (Urinary bladder, Renal Pelvis, Ureter, Urethra, Other)
- Existence of bone metastasis (Yes vs. No)
- All lesions (Investigator and BICR Assessments at baseline): sites of disease, number of disease sites per patient
- Target lesions (Investigator and BICR Assessments at baseline): presence of target lesions, site of target lesion, sum of reference diameter of target lesion (tumor burden)
- Urothelial histology
- Hepatic impairment (No [total bilirubin <= ULN and AST <= ULN] vs. Yes [total bilirubin > ULN or AST > ULN])
- Renal impairment (No [creatinine clearance >= 60 mL/min] vs. Yes [creatinine clearance < 60 mL/min]).
- Baseline laboratory test values including absolute lymphocyte count, absolute neutrophil count, hemoglobin by descriptive statistics and by category (< 10g/dL, ≥ 10g/L), platelet count, total bilirubinbilirrubinbilirubin, ALT, AST, alkaline phosphatase, creatinine, creatinine clearance.

Concordance in evaluation of PD-L1 status (PD-L1 Low, High, Unknown) between 28-8 and 22C3 assays will be provided for the Treated Population.

7.3.1 Medical and Cancer History

Cancer history will be summarized and listed for the Treated PD-L1 Low Population, Treated Population, Treated PD-L1 High Population, and will include time from initial urothelial cancer diagnosis to first dose date (<1 year vs. ⩾ 1 year), time from metastatic/advanced urothelial cancer diagnosis to first study drug dose date (<1 year vs. ⩾ 1 year), location of primary tumor at diagnosis (upper track vs. lower track), initial diagnosis classification, stage at initial disease, current TNM staging, history of brain metastases, metastases location (lymph node only, visceral), liver metastases, and historic PD-L1 status (by assay used).

Medical history collected at screening will be mapped by the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class (SOC) and preferred term for the Treated Population. For summary tables, a patient will be counted only once per SOC and preferred term.

7.3.2 Prior Systemic Cancer/Oncology Therapies

Per the protocol, an eligible patient will have received no prior systemic cancer/oncology therapies in an inoperable locally advanced/metastatic setting. All patients who received prior systemic cancer/oncology therapies in an inoperable locally advanced/metastatic setting are considered significant protocol violations.

Treatment given in the non-muscle invasive setting, such as BCG vaccine or mitomycin is not considered treatment in the advanced setting. Also, patients who have received neoadjuvant or adjuvant treatment are eligible as long as their disease did not relapse within 12 months from the last dose of treatment. Prior systemic cancer/oncology therapies will be tabulated using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) and Anatomical, Therapeutic, or Chemical Level (ATCL)-2 classifications and preferred term. If the ATCL-2 classification is missing, the next non-missing higher level of classification will be used (Level 1). If a patient reports the same medication multiple times, then the frequency of that medication will be incremented by only one in the applicable arm. As with the medication, if a patient reports multiple medications within the same ATCL-2 classification, then this patient will be counted only once in the frequency for that ATCL-2 classification in the corresponding study. Percentages will be calculated using the number of patients in the Treated Population.

The number and percent of patients who received prior therapy will be summarized. The number and percentage of patients who received cisplatin-containing, carboplatin-containing, gemcitabine-containing, or intravesical treatment will be calculated for the Treated Population. The number and percent of patients who received the setting of adjuvant, neoadjuvant, metastatic (if any) and locally recurrent regimens for locally recurrent and metastatic disease will be calculated for the Treated Population. Duration of prior therapy will be summarized descriptively. If a patient received multiple treatments of a therapy, the sum of duration will be calculated.

All prior systemic cancer/oncology therapies will be listed.

7.3.3 Surgical History and Prior Radiotherapy

Prior surgery/radiotherapy are defined as surgery/radiotherapy starting prior to the first dose.

The number and percent of patients who had prior cancer-related surgery and prior radiotherapy will be summarized by type of surgery using the Treated Population.

All prior radiotherapy and surgical procedures will be listed.

7.4 Treatments and Medications

7.4.1 Prior and Concomitant Medications

Prior and concomitant medications will be coded to ATCL and preferred drug name using WHO-DDE.

Prior medications are defined as medications taken starting prior to the first dose. Prior medications will be summarized for the Treated Population using the same analytical procedures as concomitant medications.

Concomitant medications are defined as medications taken on or after the date of first study dose, including medications initiated prior to the date of first dose and continued during treatment, and medications initiated on or after the date of first dose of study drug and within 100 days after last dose of study drug or initiation of new anticancer therapy – 1 day, whichever is earlier.

Concomitant medications will be tabulated for the Treated Population by WHO-DDE ATCL-2 classifications and preferred term. If the ATCL-2 classifications is missing, the next non-missing higher level of classification will be used (Level 1). If a patient reports the same medication multiple times, then the frequency reported for that medication will be incremented by only one. As with the medication, if a patient reports multiple medications within the same ATCL-2 classification then the frequency for that ATCL-2 classification will be incremented by only one. Percentages will be calculated using the total number of patients in the Treated Population.

For the medications initiated prior to the date of the first dose of study drug and continued during the treatment, they will be considered as both prior medications and concomitant medications.

The number of patients that received narrow therapeutic index CYP substrates as concomitant medications will also be summarized.

Prior and concomitant medications will also be presented in a data listing.

7.4.2 Concomitant Radiotherapy/ Procedures

The concomitant radiotherapy/procedures are defined as one of the following and will be coded using the MedDRA dictionary:

- Any radiotherapy/procedures with a start date prior to or on C1D1 and continued on or after C1D1
- Any radiotherapy/procedures with a start date after C1D1, but prior to or on the last dose date + 30 days and start of subsequent anticancer therapy, whichever is earlier

The number and percent of patients who had concomitant radiotherapy will be summarized by site and type of radiotherapy for the Treated PD-L1 Low Population, Treated Population, Treated PD-L1 High Population.

The number and percent of patients who had concomitant procedures will be summarized by each coded procedure preferred term for the Treated Population.

All concomitant radiotherapy and procedures will be listed.

7.4.3 Subsequent Anti-Cancer Therapy

Subsequent anti-cancer systemic therapy will be summarized for the Treated PD-L1 Low Population, Treated Population, Treated PD-L1 High Population, and tabulated using the WHO-DDE and ATCL-2 classifications and preferred term. The number and percentage of patients who took at least one subsequent anti-cancer therapy will be calculated and presented, ATCL-2 classifications, and preferred term. The number and percentage of patients who took at least one subsequent post-study immune-oncology therapy will be calculated and presented.

For patients who received GemCarbo as study treatment, if they subsequently crossed over and received the treatment of bempegaldesleukin and nivolumab, then bempegaldesleukin and nivolumab will be counted as subsequent therapy for these patients.

7.4.4 Immune Modulating Medication

The list of anatomic class, therapeutic class and generic name used for the selection of immune-modulating medication (IMM) will be provided at the time of the database lock.

The percentage of patients who received immune-modulating concomitant mediations for the following will be summarized.

- Management of drug-related select immune-related adverse events (irAEs) (any Grade, Grade 3-5) by select irAE category/subcategory (see Section 7.8.7 for select irAEs)
- Management of immune-mediated adverse events (IMAEs) (any grade, grade 3-5) by IMAE category (see Section 7.8.8 for IMAEs) will be reported by medication class and generic term.

For each category/subcategory of drug-related select irAEs (any grade, grade 3-5) and IMAEs (any grade, grade 3-5), the following will be reported:

- Total duration of IMM use (excluding overlaps), duration of high dose of corticosteroid, initial dose of corticosteroid, and tapering duration (summary statistics)

7.4.5 Study Drug Exposure

Overall exposure to study treatments and study treatment administration for all cycles combined will be summarized for Treated PD-L1 Low Population, Treated Population, and Treated PD-L1 High Population, respectively. Overall exposure to study treatments will be summarized in terms of exposure duration, number of cycles, cumulative dose and relative dose intensity. The following summaries will be performed:

- Relative dose intensity (%) using the following categories:
  $< 50\%$; $50 - < 70\%$; $70 - < 90\%$; $90 - < 110\%$; $\geq 110\%$.
- Number of patients with at least one dose delayed, number of doses delayed per patient, and the reason for dose delay.

- The number of patients with at least one dose interruption, the reason for interruption, the number of interruptions per patient, the reason for the first dose interruption and time to the first interruption per patient.
- Number of patients with at least one dose reduction of NKTR-214 along with the reason of the dose reduction, the reason for the first dose reduction of NKTR-214 and time to the first dose reduction per patient.

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

In addition, time to study regimen discontinuation will be summarized and presented using a Kaplan-Meier curve whereby the last dose date will be the event date for those patients who are off study therapy. Time to study regimen discontinuation is the same as time to last dose of either nivolumab or NKTR-214, which is defined as (the date of the last dose minus the date of the first dose + 1) / 30.4375. Median duration of study therapy and associated 95% CI will be provided. Patients who are still on study therapy will be censored on their last dose date. Time to NKTR-214 discontinuation will be summarized in the same way as well. Time to NKTR-214 treatment discontinuation is the same as time to last dose of NKTR-214, which is defined as (the date of the last dose minus the date of the first dose + 1) / 30.4375.

7.5 Efficacy Analysis

The Treated PD-L1 Low Population will be used for the primary analysis of ORR by RECIST 1.1 per BICR.

Efficacy analyses of ORR, PFS, TTR and DOR by RECIST 1.1 per BICR and per investigator and OS will be performed on the Treated PD-L1 Low Population, the Treated Population and the Treated PD-L1 High Population.

Concordance rate of ORR will be computed as the frequency with which investigator's assessment and BICR's assessment agree on classification of a subject as responder vs non-responder.

7.5.1 Analysis of Primary Endpoint: ORR by BICR in Treated PD-L1 Low Population

The primary analysis for the primary endpoint of ORR will be performed in the Treated PD-L1 Low Population per RECIST 1.1 by BICR. The 95% exact CI of ORR will be calculated by the Clopper-Pearson method (Clopper and Pearson, 1934). The number and percentage of patients in each category of BOR per BICR (confirmed complete response [CR], confirmed partial response [PR], stable disease [SD], progressive disease [PD], or not evaluable [NE]) will be presented. The complete response rate and the partial response rate and their 95% CIs will also be presented.

The primary analysis will be performed based on the data with cut-off date approximately 18 months after the last patient has been enrolled into the study.

7.5.2 Analysis of Secondary Efficacy Endpoints

7.5.2.1 ORR by BICR in the Treated Population

ORR per BICR in the Treated Population is a secondary endpoint. The analysis follows Section 7.5.1, replacing the Treated PD-L1 Low Population with the Treated Population. If the total number of patients is 175 in the Treated Population, then the null hypothesis of ORR less than 29% will be rejected in the Treated Population when the observed ORR is at least 37%.

ORR by BICR will also be calculated for BICR Measurable Disease Treated Population, alongside the 95% exact CI of ORR.

7.5.2.2 Duration of Response per BICR

DOR per RECIST v1.1 per BICR will be analyzed by the Treated PD-L1 Low Population and the Treated Population, respectively. DOR will be calculated for responders only, using the sensoring rules in Table 3. DOR will be summarized and analyzed as a time-to-event endpoint, using the Kaplan-Meier method. DOR rates $\geq$ 6, 12 and 18 months will be estimated.

DOR per BICR will also be analyzed similarly for BICR Measurable Disease Treated PD-L1 Low Population and BICR Measurable Disease Treated Population, if there are 3 or more patients with BICR BOR of CR among patients without baseline BICR measurable disease in Treated PD-L1 Low Population and in Treated Population, respectively.

7.5.2.3 ORR and DOR by Investigator in Treated PD-L1 Low Population and Treated Population

The secondary endpoint is ORR per RECIST v1.1 per investigator in the Treated PD-L1 Low Population and the Treated Population. The analysis follows Section 7.5.1, replacing BICR by investigator. DOR by investigator will be analyzed similarly using the sensoring rules in Table 3 and the Kaplan-Meier method. DOR rates $\geq$ 6, 12 and 18 months will be estimated.

7.5.3 Analysis of Exploratory Efficacy Endpoints

7.5.3.1 Progression-Free Survival by BICR and by Investigator in Treated Populations

PFS by RECIST v1.1 by BICR and by investigator will be analyzed with the Kaplan-Meier method for the Treated PD-L1 Low Population, Treated Population, and Treated PD-L1 High Population. The Kaplan-Meier method will be used to summarize PFS, including Kaplan-Meier curves, and medians with corresponding 95% CIs. The PFS rates at 3, 6 and 12 months will also be estimated. The censoring methods described in Table 3 will be used in deriving the endpoint of PFS, per BICR and per investigator, respectivley.

Table 3: PFS Analysis: Date of Progression or Censoring

Situation	Date of Disease Progression or Censoring	Outcome
No baseline assessments for tumor response	First dose date	Censored
No on study tumor assessments and no death	First dose date	Censored
Not known to have progressed or died according to data in the database as of data-cut-off date	Date of last tumor assessment showing no evidence of disease progression per RECIST 1.1	Censored
Disease progression reported on multiple response assessments or multiple scans were performed	Date of the earliest evidence of PD	Progressed
Death without PD	Date of death	Progressed

7.5.3.2 Sensitivity analysis of PFS by BICR and by Investigator

For the sensitivity analysis of PFS, the censoring methods described in Table 4 will be used in deriving the endpoint of PFS per BICR and per investigator, respectivley.

The analysis populations are the Treated PD-L1 Low Population, the Treated Population, the Treated PD-L1 High Population for PFS by BICR and by investigator.

Table 4: PFS Sensitivity Analysis: Date of Progression or Censoring

Situation	Date of Disease Progression or Censoring	Outcome
No baseline assessments for tumor response	First dose date	Censored
No on study tumor assessment and no death	First dose date	Censored
Disease progression or death after two or more consecutive missed tumor response assessments	Date of last tumor assessment showing no evidence of disease progression per RECIST 1.1 before the first missed tumor assessment	Censored
Not known to have progressed or died according to data in the database as of data-cut-off date	Date of last tumor assessment showing no evidence of disease progression per RECIST 1.1	Censored
Disease progression reported on multiple response assessments or multiple scans were performed	Date of the earliest evidence of PD	Progressed
Disease progression or death after one missed tumor response assessments	Date of the earliest evidence of PD	Progressed
Death without PD or new anti-cancer therapy	Date of death	Progressed
Starting subsequent anti-cancer therapy prior to observing PD or death	Date of last tumor assessment showing no evidence of disease progression per RECIST 1.1 on or before start date of the subsequent anti-cancer therapy	Censored

Abbreviations: PFS = progression-free survival; PD = progressive disease; RECIST = response evaluation criteria in solid tumors.

The analysis follows Section 7.5.3.1.

7.5.3.3 Concordance Between BICR and Investigator Assessment of Progression

For the purpose of assessing concordance between the BICR and investigator tumor assessments, progression status will be categorized as documented progression, death or censored. A cross tabulation between the BICR and the investigator progression status will be presented. The primary analysis of PFS will be used for this assessment.

A by patient lising of BICR and investigator PFS status and the time between progression dates according to the BICR and the investigator will be provided.

7.5.3.4 Overall Survival

The Kaplan-Meier method will be used to summarize OS, using methods similar to PFS. The OS rates ≥ 6, 12 and 18 months will also be estimated.

OS will be analyzed for the following populations:

- Treated PD-L1 Low Population
- Treated Population
- Treated PD-L1 High Population.

7.5.3.5 Current Status of PFS and OS Follow-up

The extent of follow-up defined as the time between the first dose date and last known date alive (for patients who are alive) or death date (for patients who died) will be summarized descriptively (median, minimum, maximum) in months for all treated patients.

The currentness of follow-up for survival, defined as the time between last OS contact (i.e., last known alive date or death date) and clinical data cutoff date, will be summarized in months for all treated patients. Patients who died and patients with last known alive date on or after data cutoff date will have zero value for currentness of follow-up.

The currentness of follow-up for PFS, defined as time from last evaluable tumor assessment to cutoff date will be summarized for all treated patients. Patients who have a PFS event or whose last tumor assessment date was on or after clinical cutoff date will be considered as current (zero value) for this analysis.

The currentness of follow-up will be categorized into the following categories: 0 month, 0-3 months, 3-6 months, 6-9 months, 9-12 months, and 12 or more months.

7.5.3.6 Time to Response by BICR and Investigator

TTR by BICR and by investigator will be analyzed for the following populations:

- Treated PD-L1 Low Population
- Treated Population
- Treated PD-L1 High Population.

In addition, TTR by BICR will also be similarly analyzed for the following populations:

- BICR Measurable Disease Treated PD-L1 Low Population, if there are 3 or more patients with BICR BOR of CR among patients without baseline BICR measurable disease in Treated PD-L1 Low Population

- BICR Measurable Disease Treated Population, if there are 3 or more patients with BICR BOR of CR among patients without baseline BICR measurable disease in Treated Population
- BICR Measurable Disease Treated PD-L1 High Population, if there are 3 or more patients with BICR BOR of CR among patients without baseline BICR measurable disease in Treated PD-L1 High Population.

7.5.3.7 ORR by BICR in Treated PD-L1 High Population

ORR by BICR will be analyzed for Treated PD-L1 High Population and will be summarized similar to ORR in Section 7.5.1:

ORR by BICR will also be similarly analyzed for the BICR Measurable Disease Treated PD-L1 High Population, if there are 3 or more patients with BICR BOR of CR among patients without baseline BICR measurable disease in Treated PD-L1 High Population.

7.5.3.8 DOR by BICR and by Investigator in the Treated PD-L1 High Population

DOR by BICR and by investigator in the Treated PD-L1 High Population will be analyzed based on the Kaplan-Meier method, using the sensoring rules in Table 3.

DOR per BICR will also be analyzed similarly for BICR Measurable Disease Treated PD-L1 High Population, if there are 3 or more patients with BICR BOR of CR among patients without baseline BICR measurable disease in Treated PD-L1 High Population.

7.5.3.9 ORR and DOR in BICR Efficacy Evaluable Population

ORR per BICR will be analyzed in the BICR Efficacy Evaluable Population for patients in the Treated PD-L1 Low Population, Treated Population, and Treated PD-L1 High Population, respectively.

DOR per BICR will also be analyzed similarly for BICR Efficacy Evaluable Population using the sensoring rules in Table 3, if there are 3 or more patients with BICR BOR of CR among patients without baseline BICR measurable disease in Treated PD-L1 Low Population, Treated Population, and Treated PD-L1 High Population, respectively.

7.5.3.10 Clinical Benefit Rate by BICR and Investigator

CBR by BICR and by investigator will be analyzed for the following populations:

- Treated PD-L1 Low Population
- Treated Population
- Treated PD-L1 High Population

CBR by BICR and by investigator will be summarized similar to ORR.

7.5.4 Subgroup Analyses

The subgroup analyses will be performed for ORR, PFS by RECIST 1.1 per BICR per the Treated PD-L1 Low Population and Treated Population, when appropriate. All subgroups are created based on baseline values.

The following subgroup analyses (except age, race, region, and gender) will be conducted if the number of patients in each subgroup is more than 10, regions with less than 10 patients will be grouped into the 'other' category.

- Age ($< 65, \geq 65; < 75, \geq 75$)
- Gender (male, female)
- Race (White, Black or African American , Asian, other)
- Time from initial urothelial cancer diagnosis to first dose date (<1 year, $\geq$ 1 year)
- Patients with history of brain metastases (Yes, No)
- Geographic region (US/Canada, Europe, Rest of World)
- ECOG Performance status
- Tumor burden at baseline per BICR and per investigator (<= 1st Tertile, > 1st Tertile to <= 2nd Tertile, >2nd Tertile).
- Disease location (locally advanced disease only, metastatic disease)
- Metastases location (lymph node only, visceral disease)
- Liver metastases (present, absent)
- Location of the primary tumor at diagnosis (Upper urinary tract, Lower urinary tract)
- Existence of bone metastasis (Yes, No)
- Reason for cisplatin ineligibility
    - Eastern Cooperative Oncology Group (ECOG) performance status of 2 or above
    - Creatinine clearance less than 60 mL/min
    - Grade $\geq$ 2 hearing loss
    - Grade $\geq$ 2 neuropathy
- Neoadjuvant or adjuvant chemotherapy (Yes, No)

Similar subgroup analysis will be performed for these endpoints based on investigator assessment. Similar subgroup analysis of OS will be performed as well when appropriate.

7.6 Health-Related Quality of Life (HRQoL)

Patients will be asked to complete the 3-level version of the EuroQol Group's EQ-5D (EQ-5D-3L), EORTC QLD-C30, and GP5 during screening, after enrolment but prior to first dose, at on-study clinic visits occurring q3w while on treatment, and at follow-up visits 1 and 2. In addition, the EQ-5D-3L will be completed via telephone during the survival follow-up phase.

7.6.1 EQ-5D-3L

The EQ-5D-3L is a standardized instrument used to measure self-reports of health status and functioning. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, as described by the EQ-5D-3L. Altogether, the instrument describes $3^5 = 243$ health states (EuroQol, 1990).

Empirically-derived weights can be applied to an individual's responses to the EQ-5D-3L descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for the UK, US, Spain, Germany, and numerous other populations. Utility index values range from a 1 (full health) to 0 (dead) with negative values indicating a state considered worse than being dead. In addition, the EQ-5D-3L includes a visual analog scale (VAS) that allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health. The EQ-5D-3L uses a recall period of "today." The mean, standard deviation, median, minimal, maximum of scores will be used to summarize EQ-5D-3L VAS.

The responses from each of 5 dimensions will be combined in a 5-digit number describing the respondent's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score. The proportion of patients within each status will be calculated and summarized.

7.6.2 EORTC Quality of Life Questionnaire

The EORTC Quality of Life Questionnaire (EORTC QLQ-C30) is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 comprises six functional scales (physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning, and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status and global quality of life items, responses for all items are 4-point categorical scales ranging from 0 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales. Raw scores

will be transformed using a linear transformation to standardize the results such that scores range from 0 to 100.

The calculation for scoring these scales is the same in all cases:

1. Calculate the average of the items that contribute to the scale; this is the raw score.
2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Calculations for raw score and linear transformation are as follows:

In practical terms, if items $I_1, I_2, \ldots I_n$ are included in a scale, where n is number of items in the scale, the procedure is as follows:

Raw score

$RS\ (Raw\ Score) = (I_1 + I_2 + I_3 + \ldots + I_n)/n$

Linear transformation

Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $S = \{1 - (RS - 1)/range\} \times 100$

Symptom scales / items: $S = \{(RS - 1)/range\} \times 100$

Global health status / QoL: $S = \{(RS - 1)/range\} \times 100$

Range is the difference between the maximum possible value of *RS* and the minimum possible value.

Raw score and linear transformed score will be calculated when at least 50% of the items from the scale have been answered. Otherwise, the score will be set as missing.

The structure of this questionnaire and scoring are presented in Table 5.

Table 5: Scoring for QLQ-C30 version 3.0

Scale	Scale abbreviation	Number of items	Individual score range	Item Number
Global health status / QoL				
Global health status/QoL	QL	2	1-7	29, 30
Functional scales				
Physical functioning	PF	5	1-4	1 to 5
Role functioning	RF	2	1-4	6, 7
Emotional functioning	EF	4	1-4	21 to 24
Cognitive functioning	CF	2	1-4	20, 25
Social functioning	SF	2	1-4	26, 27
Symptom scales / items				
Fatigue	FA	3	1-4	10, 12, 18
Nausea and vomiting	NV	2	1-4	14, 15
Pain	PA	2	1-4	9, 19
Dyspnea	DY	1	1-4	8
Insomnia	SL	1	1-4	11
Appetite loss	AP	1	1-4	13
Constipation	CO	1	1-4	16
Diarrhea	DI	1	1-4	17
Financial difficulties	FI	1	1-4	28

At each assessment point and within each subscale on the EORTC QLQ-C30, the mean, standard deviation, the median, lowest and highest scores at each visit, and change from baseline will be summarized.

7.6.3 GP5 Question

Treatment burden will be assessed by GP5, which consists of the single question: “I am bothered by side effects with treatment,” reported on a 5-point Likert scale.

The frequency and proportion of each score at each assessment point will be summarized.

7.7 Immunogenicity

7.7.1 Immnogeneicity Measurements and Endpoints

Further details on immunogenicity background and rationale, definitions, population for analyses and endpoints will be described in separate immunogenicity analysis plans for bempegaldesleukin and nivolumab. In summary, the immunogenicity analysis will be performed separately for bempegaldesleukin and nivolumab. The data will be summarized for

anti-NTKR-214/anti-PEG, anti-IL-2 and anti-nivolumab antibodies and will be reported by sample and patient status.

For sample status, baseline samples will be classified as baseline ADA-positive, if ADA is detected (positive seroconversion) in the immunogenicity sample collected before initiation of the treatment and baseline ADA-negative, if ADA is not detected in the immunogenicity sample collected before initiation of the treatment. ADA samples will be classified as positive if after initiation of the treatment, the ADA is detected in a sample from a subject who was baseline negative, or if there is at least 4-fold or greater (≥) increase in ADA titer in comparison to the baseline positive titer. Samples confirmed to be positive for anti-NKTR-214/anti-PEG, anti-IL-2 antibodies will be tested for neutralizing activity for IL-2 using a validated cell-based assay. Anti-nivolumab antibodies positive samples will also be tested for neutralizing activity for nivolumab using a validated cell-based assay. ADA positive samples with neutralizing activity will be classified as neutralizing positive.

For patient status, immunogenicity will be reported by summarizing the number and percentage of ADA-positive patients and ADA-negative patients at baseline and after drug administration with positive status of anti-NKTR-214, anti-PEG, anti-IL-2 and anti-nivolumab ADA. In the immunogenicity evaluable population, the patients will be classified as treatment-induced ADA-positive if they were ADA-negative at baseline and became ADA-positive at any time after starting the treatment, or if they were ADA-positive at baseline and had a post-baseline ADA-positive titer that was at least 4-fold or greater (≥) than baseline positive titer (Treatment-boosted). Treatment-emergent ADA-positive patients will be the sum of treatment-induced and treatment-boosted ADA-positive patients. The patients with an ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart will be classified as persistent positive. Patients that are not persistent positive but have an ADA-positive sample at the last sampling time point will be classified as not persistent last-sample positive. Non persistent positive patients with an ADA-negative sample at the last sampling time point will be classified as transiently positive or other positive. Patients with at least one ADA-positive sample with neutralizing activity will be classified as neutralizing positive. All other ADA-evaluable patients are considered as treatment-emergent ADA negative.

All ADA-positive patients will be included in the ADA titer kinetics analysis. Summary statistics of patient-level ADA titers using the maximum titer value within an ADA-positive patient will be presented for baseline ADA-negative patients and baseline ADA-positive patients. The median, interquartile range, and range of the maximum titers will be reported. For ADA-positive patients with a baseline ADA-positive sample, the median and interquartile range of the fold increase from baseline in titer (ratio of maximum post-baseline titer to baseline titer) will also be reported. For sample-level ADA titers, boxplots of ADA titers at each assessment timepoint will be provided, as appropriate, to demonstrate whether the ADA levels tend to change over time during the treatment, along with ADA incidence at each assessment timepoint.

Analyses of ADA kinetics on onset and duration will include only those ADA-positive patients that were ADA-negative at baseline. ADA-positive patients with a baseline ADA-positive

sample and an increased titer post-baseline will be excluded since this type of immune response differs mechanistically.

Onset of ADA refers to the time period between the first dose of the treatment and the first instance of ADA detection. The median, interquartile range, and range of time to ADA development will be provided. The median and range of the number of treatment doses to before and after the first detection of ADA as well as the total number of doses received will also be provided.

Duration of ADA refers to the longevity of ADA and is defined as the time from the first on-study ADA-positive date to the first ADA-negative date after the last on-study ADA-positive date. Duration of ADA will be estimated by Kaplan-Meier method. Patients who do not have an ADA-negative date after the last on-study ADA-positive date will be censored on the date of their last ADA-evaluable assessment. The median together with 95% confidence interval (using log-log transformation method) and range (min, max) will be provided.

7.7.2 Safety, Efficacy and PK Evaluation of ADA

The following analyses will be conducted for anti-NKTR-214/anti-PEG, anti-IL-2 and anti-nivolumab, separately.

- Safety: All patients with ADA as mentioned above will be assessed for potential infusion related reactions under NKTR-214 safety events and will be compared against ADA negative patients, where infusion related reaction events that start after study drug administration on the same day or next day will be included.
- Efficacy: Objective response rate will be presented by ADA status.
- Concentration: Pre-dose NKTR-214 RC and pre-dose NKTR-214 AC cncentrations will be summarized by ADA status.

7.7.3 Definitions

There are two sets of definitions: one for categorizing individual samples (Table 6) and another for categorizing patient responses (Table 7).

Table 6: ADA Status: Individual Samples

ADA Status	Definition
Baseline Negative	ADA is not detected in the last sample before initiation of treatment
Baseline positive	ADA is detected in the last sample before initiation of treatment
Anti-NKTR-214 ADA-positive sample	After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a patient for whom anti-NKTR-214 ADA is not detected at baseline, *or* (2) an ADA detected sample with anti-NKTR-214 titer to be at least 4-fold or greater (≥) than baseline positive titer
Anti-PEG ADA-positive sample	Sample with a positive result in PEG -specificity assay.
Anti-IL-2 ADA-positive sample	After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a patient for whom anti-IL-2 ADA is not detected at baseline, *or* (2) an ADA detected sample with anti-IL2 titer to be at least 4-fold or greater (≥) than baseline positive titer
Anti-nivolumab ADA-positive sample	After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a patient for whom anti-nivolumab ADA is not detected at baseline, *or* (2) an ADA detected sample with anti-nivolumab titer to be at least 4-fold or greater (≥) than baseline positive titer

Table 7: ADA Response Categories: Patient Level

ADA status	Description
Baseline ADA-positive	A patient with baseline ADA-positive sample
ADA-Negative Patient	Patient with no ADA-positive sample after the initiation of treatment. **Note:** due to the definition of an ADA positive sample for a patient testing positive at baseline (see sample status table, above), it is possible (but highly unlikely) for a patient with a stable anti-drug titer throughout the study to be classified as 'ADA-negative'
ADA-Positive Patient (Treatment-Emergent positive)	Patient with at least 1 ADA positive-sample (relative to baseline) at any time after initiation of treatment
Persistent positive	ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are **at least 16 weeks** apart (Endogenous human IgG1, IgG2, and IgG4 have approximate half-lives in the range of 21-25 days, and 5 half-lives are approximately equal to 16 weeks)
Not PP-Last Sample Positive	Not persistent positive with ADA-positive sample at the last sampling time point
Transiently positive or Other positive	Patient not persistently positive but has 1 or more ADA positive samples with the last sample being ADA-negative.
Neutralizing positive	At least 1 ADA-positive sample with neutralizing antibodies detected

Abbreviation: PP = persistent positive

7.8 Safety Analysis

Unless otherwise specified, the primary population for safety will be the Treated Population. AEs will be summarized by Treatment-Emergent Adverse Events (TEAE) defined as following:

TEAEs are AEs with onset date (and time, if collected and not missing) within the treatment-emergent period or the extended treatment-emergent period depending on the analysis, including

- Any AE that happens on or after treatment initiation
- AE that was present prior to or 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.

7.8.1 General Methods for Safety Analyses

7.8.1.1 Adverse Events, Serious Adverse Events, Multiple events

Drug-related TEAEs are those events with relationship to study drug "Related", as recorded on the CRF, specifically, NKTR-214 related TEAEs are those events with relationship to NKTR-214 "Related". If the relationship to study drug is missing, the TEAE will be considered as drug-related.

Serious TEAEs consist of TEAEs deemed serious by the Investigator and flagged accordingly in the CRF and clinical database.

TEAEs leading to study drug discontinuation are TEAEs with action taken regarding study drug(s) = "Drug Withdrawn".

A TEAE is considered as leading to treatment delay, reduction or interruption if reported as leading to the dose delay, reduction or interruption of any study drug.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the most recent version of the dictionary at the time of the database lock will be used. Adverse events results will be graded for severity using NCI Common Terminology Criteria for Adverse Events (CTCAE) and the most recent version of the criteria at the time of the database lock will be used.

In the TEAE summary tables, unless otherwise specified, patients will be counted only once at the Preferred Term (PT), only once at the System Organ Class (SOC), and only once at subject level for the counting of total number of patients with a TEAE. The TEAE tables will be sorted

by the SOCs and then PTs. SOC will be ordered by descending frequency overall and then alphabetically. PTs will be ordered within SOC by descending frequency overall and then alphabetically.

Unless otherwise specified, the TEAE summary tables will be restricted to events within the treatment-emergent period regardless of the causality.

7.8.1.2 Select Immune-Related Adverse Events (irAEs) for Checkpoint Inhibitors (to support EU MAA)

The select irAEs consist of a list of preferred terms grouped by specific category (e.g., pulmonary events, gastrointestinal events categories, etc.). Select irAEs are identified based on the following 4 guiding principles:

- AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies
- AEs that may require immunosuppression (e.g., corticosteroids) as part of their management
- AEs whose early recognition and management may mitigate severe toxicity
- AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization.

Based on these guiding principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are currently considered to be select irAEs. Multiple event terms that may describe each of these are grouped into endocrine, gastrointestinal (GI), hepatic, pulmonary, renal, and skin select irAE categories, respectively.

Hypersensitivity/infusion reactions are analyzed along with the select irAE categories because multiple event terms may be used to describe such events and pooling of terms was therefore necessary for full characterization. Hypersensitivity/infusion reactions do not otherwise meet criteria to be considered select irAEs.

The list of MedDRA preferred terms used to identify select irAEs is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock will be provided by categories/subcategories.

In addition to the frequency and worst severity of select irAEs, time-to onset, time-to resolution, and time-to resolution where immune-modulating medication was initiated will be analyzed for each specific category/subcategory of drug-related select irAEs when applicable.

Further details on the definitions of select immune-related adverse event, time-to onset and time-to resolution are described in Appendix 1.

7.8.1.3 Other ImmuneImmnue-Related Adverse Events of Special Interest (OirAESIs) for Checkpoint Inhibitors

Other immune-related events of special interest (OirAESIs) for checkpoint inhibitors consist of a list of preferred terms grouped by specific category (e.g., Myositis Event, Myocarditis Event, Demyelination Event, Guillain-Barre Syndrome, Pancreatitis Event, Uveitis Event, Encephalitis Event, Myasthenic Syndrome, Rhabdomyolysis Event, Graft Versus Host Disease).

The list of MedDRA preferred terms used to identify OirAESI is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.8.1.4 Immune-Mediated Adverse Events (IMAEs) for Checkpoint Inhibitors (to support US BLA)

Immune-mediated AEs (IMAE) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. To be specific, IMAEs are events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator that meet the definition summarized below:

- those occurring within extended treatment-emergent period,
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine AEs such as adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication),
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component

The list of MedDRA preferred terms used to identify IMAEs is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.8.1.5 Adverse Events of Special Interest and Other Safety Observations for Bempegaldesleukin

In order to further characterize AEs of special interest for bempegaldesleukin, the following categories of events have been defined. Each category is defined based on a list of preferred

terms. The preferred terms used for the selection at the time of the database lock by categories will be provided.

Adverse Events of Special Interest (AEOSI)

The AEOSI 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.

Other Safety Observations (OSO) for Bempegaldesleukin

Other safety observation (OSO) consists of a list of specific safety events for NKTR-214 that will be identified based on Sponsor-denfined terms/criteria:

- IL-2 mediated AEs
  - Flu-like symptoms
  - Rash and pruritus
  - Fatigue/asthenia
  - Arthralgia
  - Elevated hepatic transaminases
  - Elevated serum creatinine
  - Eosinophilic disorders
  - Hypotension (HoTN)
  - Syncope
- Infusion-related reaction (IRR, same day or next day post study drug administration)
- Cytokine release syndrome (CRS)/cytokine storm
- Capillary leak syndrome (CLS)
- Tachyarrhythmias (including supraventricular and ventricular)

7.8.2 Deaths

Deaths will be summarized:

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

A by-subject listing of deaths will be provided for bempegaldesleukin/nivolumab and GemCarbo Treated Populations.

7.8.2.1 Adverse Events Leading to Death

AEs leading to death are defined as AEs with an AE Grade 5 and/or an AE outcome='Fatal'. AEs leading to death will be summarized as follows:

- AEs leading to death by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.
- Any drug-related AEs leading to death by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.
- NKTR-214 related AEs leading to death by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.

This summary will include all events that occurred on or after the date and time of the first dose of study treatment (i.e., no safety window).

A listing of patients with AE leading to death will also be provided.

7.8.3 Serious Treatment-emergent Adverse Events

Serious adverse events will be summarized:

- SAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.
- Any drug-related SAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.
- NKTR-214 related SAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.

All analyses will be conducted using the treatment-emergent period. A by-subject SAE listing will be provided for the “enrolled patients” population.

7.8.4 Treatment-emergent Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation will be summarized as follows:

- AEs leading to discontinuation of any study drug by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.
- Any drug-related AEs leading to discontinuation of any study drug by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.
- AEs leading to discontinuation of bempegaldesleukin by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.

- NKTR-214 related AEs leading to discontinuation of bempegaldesleukin by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.

The analyses will be conducted using the treatment-emergent period. A by-subject AEs leading to discontinuation listing will be provided.

7.8.5 Treatment-emergent Adverse Events Leading to Dose Modification

AEs leading to dose delay/reduction/interruption will be summarized as follows:

- AEs leading to dose reduction of bempegaldesleukin by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.
- NKTR-214 related AEs leading to dose reduction of bempegaldesleukin by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.
- Any drug-related AEs leading to dose reduction of bempegaldesleukin by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.
- AEs leading to infusion interruption of any study drug presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT
- AEs leading to infusion interruption of bempegaldesleukin presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT

The analysis will be conducted using the treatment-emergent period. A by-subject AEs leading to dose delay/reduction/infusion interruption listing will be provided.

7.8.6 Treatment-emergent Adverse Events

Adverse events will be summarized.

The following analyses will be conducted using the treatment-emergent period only:

- Overall summary of TEAEs.
- Summary of all TEAEs by SOC/PT.
- TEAEs presented by worst CTC grade (any grade, Grade 3-4, Grade 5) by SOC/PT.
- Grade 3 and above TEAEs presented by SOC/PT.
- Any drug-related TEAEs presented by worst CTC grade (any grade, Grade 3-4, Grade 5) by SOC/PT.
- NKTR-214 related TEAEs presented by worst CTC grade (any grade, Grade 3-4, Grade 5) by SOC/PT.
- Grade 3 and above any drug-related TEAEs presented by SOC/PT.
- Grade 3 and above NKTR-214 related TEAEs presented by SOC/PT.
- Serious TEAEs presented by worst CTC grade (any grade, Grade 3-4, Grade 5) by SOC/PT.

- Serious any drug-related TEAEs presented by worst CTC grade (any grade, Grade 3-4, Grade 5) by SOC/PT.
- Serious NKTR-214 related TEAEs presented by worst CTC grade (any grade, Grade 3-4, Grade 5) by SOC/PT.
- TEAEs that required immune-modulating medication by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.

The following analyses will be conducted using the treatment-emergent period and repeated using the extended treatment-emergent period:

- Any drug-related TEAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.
- NKTR-214 related TEAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by SOC/PT.

A by-subject AE, serious AE, grade 3 and above TEAEs listings will be provided..

7.8.7 Select Immune-Related Adverse Events (irAEs) for Checkpoint Inhibitors (to support EU MAA)

Unless otherwise specified, analyses will be performed by select irAEs category. Analyses will also be repeated by subcategory of endocrine events.

7.8.7.1 Incidence of Select irAEs

Select irAEs will be summarized for each category/subcategory.

The following analyses will be conducted using the treatment-emergent period only:

- Overall summaries of any select irAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category or Subcategory/PT.
- Overall summaries of any drug-related select irAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category or Subcategory/PT.
- Overall summaries of any serious select irAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category or Subcategory /PT.
- Overall summaries of drug-related serious select irAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category or Subcategory /PT.
- Overall summaries of any select irAEs leading to discontinuation of any agent by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category or Subcategory /PT.
- Overall summaries of drug-related select irAEs leading to discontinuation of any agent by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category or Subcategory /PT.
- Summary of frequency of unique select irAEs by Category.

A by-subject select irAE listing will be provided.

7.8.7.2 Time-to Onset of Select irAEs

Time-to onset of drug-related select irAEs (any grade, Grade 3-5) will be summarized for each category/subcategory.

Time-to onset analyses are restricted to treated patients who experienced at least one drug-related select irAE in the category/subcategory. The analyses will be conducted using the treatment-emergent period.

Additional details regarding the time-to onset definition are described in time-to onset definition subsection of Appendix 1.

7.8.7.3 Time-to Resolution of Select irAEs

Time-to resolution of the following specific events will be summarized separately for each category/subcategory.

- Time-to resolution of drug-related select irAEs (any grade, Grade 3-5)
- Time-to resolution of drug-related select irAEs (any grade, Grade 3-5) where immune-modulating medication was initiated.

Time-to resolution analyses are restricted to treated patients who experienced the specific events. Time-to resolution where immune-modulating medication was initiated analyses are restricted to treated patients who experienced the specific events and who received immune-modulating medication during the longest select irAE.

The analyses will be conducted using the treatment-emergent period.

The following summary statistics will be reported: percentage of patients with resolution of the longest select irAE, median time-to resolution along with 95% CI (derived from Kaplan-Meier estimation) and ranges.

See time-to resolution definition subsection of Appendix 1 for additional details.

7.8.8 Immune-Mediated Adverse Events for Checkpoint Inhibitors (to support US BLA)

IMAEs will be summarized for each immune-mediated category using the extended treatment-emergent period as follows:

- Overall summary of non-endocrine IMAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) where immune-modulating medication was initiated presented by Category / PT.

- Overall summary of endocrine IMAEs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category / PT.
- Overall summary of non-endocrine IMAEs leading to discontinuation of any agent by worst CTC grade (any grade, Grade 3-4, Grade 5) where immune-modulating medication was initiated presented by Category / PT.
- Overall summary of endocrine IMAEs leading to discontinuation of any agent by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category / PT.
- Overall summary of non-endocrine IMAEs leading to dose delay or reduction by worst CTC grade (any grade, Grade 3-4, Grade 5) where immune-modulating medication was initiated presented by Category / PT.
- Overall summary of non-endocrine IMAEs leading to dose delay by worst CTC grade (any grade, Grade 3-4, Grade 5) where immune-modulating medication was initiated presented by Category / PT.
- Overall summary of non-endocrine IMAEs leading to dose reduction by worst CTC grade (any grade, Grade 3-4, Grade 5) where immune-modulating medication was initiated presented by Category / PT.
- Overall summary of endocrine IMAEs leading to dose delay or reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT.
- Overall summary of endocrine IMAEs leading to dose delay by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category / PT.
- Overall summary of endocrine IMAEs leading to dose reduction by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category/PT.
- Summaries of time-to onset and time-to resolution of non-endocrine IMAEs where immune-modulating medication was initiated presented by Category.
- Summaries of time-to onset and time-to resolution of endocrine IMAEs presented by Category.

A by-subject listing of IMAEs will be provided. By-subject listings of time-to resolution for longest IMAEs cluster (any grade and grade 3-5 in separate summaries) will also be provided.

7.8.9 Other Immune-Related Adverse Events of Special Interest (OirAESIs) for Checkpoint Inhibitors

OirAESIs will be summarized for each category.

The following analyses will be conducted using the extended treatment-emergent period:

- Overall summary of OirAESIs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category / PT

- Overall summary of drug-related OirAESIs by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by Category / PT

A by-subject listing of OirAESIs will be provided.

7.8.10 Adverse Events of Special Interest for Bempegaldesleukin

7.8.10.1 Adverse Events of Special Interest

The following analyses will be conducted for ICE:

- Overall summary of ICE by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by PT
- Overall summary of any serious ICE by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by PT
- Overall summary of any ICE leading to discontinuation of study therapy by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by PT
- Overall summary of any ICE leading to discontinuation of bempegaldesleukin by worst CTC grade (any grade, Grade 3-4, Grade 5) presented by PT
- Time-to onset of ICE (any grade, Grade 3-5)
- Exposure-adjusted incidence rate for ICE events by Category/PT

Time-to onset analyses are restricted to treated patients who experienced at least one ICEs.

A by-subject listing of ICE will be provided.

7.8.10.2 Other Safety Observations (OSO) for Bempegaldesleukin

Table 8 lists the planned analyses for each category of OSO for bempegaldesleukin defined in Section 7.8.1.5.

Those analyses will be summarized as treated for each category (if applicable)/PT using the treatment-emergent period.

1) Overall summary of OSO by worst CTC grade presented by category/PT (any grade, Grade 3-4, Grade 5).
2) Overall summary of serious OSO by worst CTC grade presented by category/PT (any grade, Grade 3-4, Grade 5).
3) Overall summary of OSO leading to discontinuation of any study drug by worst CTC grade presented by category/PT (any grade, grade 3-4).
4) Overall summary of OSO leading to discontinuation of bempegaldesleukin by worst CTC grade presented by category/PT (any grade, Grade 3-4).

5) Time-to onset of OSO (any grade, Grade 3-5) by category

6) Overall summary of OSO by Cycle by worst CTC Grade by category (any grade, Grade 3-5)

Cycle is defined based on bempegaldesleukin administration. For patients who discontinue bempegaldesleukin but continue on nivolumab, remaining cycles will be derived based on nivolumab administration.

Time-to onset analyses are restricted to treated patients who experienced at least one OSO in the specific category.

For IRR, events that start after study drug administration on the same day or next day will be included. If AE onset time is available, the time information will be used to exclude events that start before study drug administration; otherwise, AEs that start on the same day as study drug administration will be included.

A by-subject listing of OSO will be provided.

Table 8: Planned Analyses for OSO for Bempegaldesleukin

Table Numbers[a]	Tachyarrhythmias	Syncope	CRS CLS	Infusion-related reaction (same day or next day post study drug administration)	Flu-like symptoms; Rash and pruritus; Fatigue/asthenia; Arthralgia; Elevated hepatic transaminases; Elevated serum creatinine; Eosinophilic disorders; Hypotension
1), 2)	Yes	No	No	Yes	Yes
3), 4)	Yes	No	No	Yes	Yes
5)	Yes	Yes	Yes	Yes	Yes
6)	No	Yes	No	Yes	Yes

Abbreviations: CLS = capillary leak syndrome; CRS = cytokine release syndrome/cytokine storm
a. Table description provided in Section 7.8.10.2

7.8.11 Adverse Events by Subgroup

Overall summary of TEAEs and TEAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT in the Treated Population will be provided for the following subgroups:

- Gender (Male, Female)
- Race (White, Black or African American, Asian, other)
- Age category (< 65, ≥ 65)

- Geographic region (US/Canada, Europe, Rest of World)
- Hepatic impairment (No [total bilirubin <= ULN and AST <= ULN], Yes [total bilirubin > ULN or AST > ULN])
- Renal impairment (No [creatinine clearance >= 60 mL/min], Yes [creatinine clearance < 60 mL/min]).

These analyses will be conducted using the treatment-emergent period only.

7.9 Laboratory Parameters

The analysis population for each laboratory test is restricted to Treated Population who underwent that laboratory test.

7.9.1 Hematology

The following will be summarized as baseline CTC grade and worst CTC grade during treatment-emergent period per subject: hemoglobin (HGB), platelet counts (PLAT), white blood counts (WBC), absolute neutrophils count (ANC) and absolute lymphocyte count (LYMPH). A table presenting number and percentage of patients with post-baseline CTC grade worsened from baseline (any grade, Grade 3-4) will be provided.

The analyses will be conducted using the treatment-emergent period.

A by-subject listing of these laboratory parameters will be provided.

Eosinophil (EOS)

- Summary of baseline and highest post-baseline EOS will be provided:
  - Mean(SD), median, min and max
  - Percent exceeding thresholds: $\geq 10x10^9/L$, $\geq 5x10^9/L$, $\geq 1.5x10^9/L$
  - Time to highest post-baseline EOS: mean (SD), median, min, max
  - Duration (Weeks) of Sustained Eosinophils $\geq 1.5x10^9/L$: % of subjects with eosinophils returned, % subjects with duration longer than 6 months, median and 95%CI will be estimated using the KM method

Plot of mean eosinophil (± SE) by time.

7.9.2 Serum Chemistry

The following will be summarized as baseline CTC grade and worst CTC grade during treatment-emergent period per subject: ALT, AST, alkaline phosphatase (ALP), total bilirubin, creatinine, amylase and lipase. A table presenting number and percentage of patients with worst post-baseline abnormalities worsened from baseline (any grade, Grade 3-4) will be provided.

The analyses will be conducted using the treatment-emergent period.

A by-subject listing of these laboratory parameters will be provided.

7.9.3 Electrolytes

The following will be summarized as baseline CTC grade and worst CTC grade in treatment-emergent period per subject: sodium (high and low), potassium (high and low), calcium (high and low), and glucose. A table presenting number and percentage of patients with worst post-baseline abnormalities worsened from baseline (any grade, Grade 3-4) will be provided.

The analyses will be conducted using the treatment-emergent period.

A by-subject listing of these laboratory parameters will be provided.

7.9.4 Additional Analyses

In addition, further analyses on specific laboratory parameters will be performed:

Abnormal Hepatic Function Test

The number of patients with the following laboratory abnormalities from evaluations during the treatment-emergent period will be summarized:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- ALP > 1.5 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN and all ALP measurements normal or < 2 x ULN

For identification of concurrent elevations, window for identification of total bilirubin elevation applies to on or after ALT/AST elevation. Window for ALP applies to both before and after ALT/AST elevation.

The analyses will be conducted using the extended treatment-emergent period.

A by-subject listing of these specific abnormalities will be provided.

Abnormal Thyroid Function Test

The number of patients with the following laboratory abnormalities from evaluations during the treatment-emergent period will be summarized:

- TSH value > ULN and
  - with baseline TSH value ≤ ULN
  - with at least one FT3/FT4 test value < LLN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≥ LLN within 2-week window after the abnormal TSH test
  - with FT3/FT4 missing within 2-week window after the abnormal TSH test.
- TSH < LLN and
  - with baseline TSH value ≥ LLN
  - with at least one FT3/FT4 test value > ULN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≤ ULN within 2-week window after the abnormal TSH test
  - with FT3/FT4 missing within 2-week window after the abnormal TSH test

The analyses will be conducted using the treatment-emergent period.

A by-subject listing of these specific abnormalities will be provided.

7.10 Vital Signs

Values at each scheduled visit, change, and percent change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, respiration rate, and body temperature will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 9 below. Abnormal values for patients exhibiting clinically notable vital sign abnormalities will be listed. Alert vital signs are defined as an absolute value outside the defined range and percentage change > 25%. The abnormal values for patients exhibiting alert vital sign abnormalities will be listed.

Table 9: Criteria for Clinically Notable Vital Sign Abnormalities

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

8.0 COVID-19 RELATED ANALYSES

A brief high-level summary of patients impacted by COVID-19 will be provided for the Treated Population. This summary will present the number and percentage of patients with any incidence in each of the categories listed below due to COVID-19 and any reason, where total number of patients will be used as denominator for percentage calculation:

- Any positive test of COVID-19
- Received COVID-19 vaccine (type/manufacturer of vaccine, e.g. mRNA vaccine from Pfizer) during treatment
- Missed study visit
- Missed at least 2 consective doses
- Delayed tumor assessment scan
- Missed tumor assessment scan (any missed scan, 2 scans missed, ≥ 3 scans missed)
- Study treatment discontinuation
- Study discontinuation
- Death

A by-subject listing of incidences in each category due to COVID-19 will be provided.

Number of unique incidences per person in each of the categories listed below due to COVID-19 will be summarized by country (site) using descriptive statistics:

- Missed study visit
- Missed at least 2 consective doses
- Delayed tumor assessment scan
- Missed tumor assessment scan.

A table showing total number of occurrences (unique incidences) in each category will be provided.

8.1 Impacts on Efficacy Results

Supplementary analyses for ORR and DOR may be performed to estimate the treatment effects without the COVID-19 impact if needed.

8.2 Impacts on Safety Results

By-patient listing for COVID-19 related adverse events will be provided for the Treated Population. If sample size allows (e.g. >10), COVID-19 related TEAEs can be summarized by worst CTC grade for COVID-19 infected patients. Impact of COVID-19 vaccines on study drug dosing and adverse events may be further explored.

If central clinical laboratory data was missing for some patients in some visits due to COVID-19, local laboratory data may be collected in place of missed central laboratory data. In such a case, central laboratory and local laboratory data may be combined for the lab related analysis. Specifical considerations are described as follows:

1. For summary of post-baseline laboratory toxicity worsening from baseline

   All (scheduled and unscheduled) central and local laboratory data will be included. The central and local laboratory data will be graded according to their corresponding laboratory normal ranges (central laboratory normal range for central laboratory data, local laboratory normal range for local laboratory data). If the baseline value is involved in the derivation of toxicity grade, the corresponding baseline value for central and local laboratory will be used as reference (central laboratory toxicity grade based on central laboratory baseline value, local laboratory toxicity grade based on local laboratory baseline value). If a corresponding baseline value is not available, for that particular laboratory value, the toxicity grade will be derived assuming the baseline value is normal, thus the grade will be derived based on corresponding normal range only.

   In summary table, the baseline toxicity grade will be based on central laboratory data if the central laboratory data is available; otherwise (central laboratory data is not available), then the baseline grade will be based on local laboratory if available. The post-baseline worst toxicity grade will be based on the worst grade of both central and local laboratory data.

2. For summary of abnormal hepatic fuction and summary of abnormal thyroid function

   All (scheduled and unscheduled) central and local laboratory data will be included. The central and local laboratory data (AST, ALT, BILI, TSH, FT3, FT4) will be summarized according to their corresponding laboratory normal ranges (central laboratory normal range for central laboratory data, local laboratory normal range for local laboratory data).

9.0 DATA MONITORING COMMITTEE

This study is monitored by an IDMC, comprised of qualified clinicians and a biostatistician, all independent from the Sponsor and (for the clinicians) independent of investigational sites, selected to avoid conflict(s) of interest. The IDMC will assess accumulating safety data and emerging risk/benefit balance at regular intervals and on an ad-hoc basis. The first planned IDMC safety review will occur after the first 20 patients receiving bempegaldesleukin/nivolumab have been treated for 6 weeks. Details are provided in the IDMC charter.

The IDMC's specific activities will be detailed in a mutually agreed upon charter, which will define the relevant processes, including meeting proceedings and structure, data assessments, documentation and recordkeeping, process for IDMC recommendations, and regulatory

reporting, as applicable. The charter will contain procedures to ensure the minimization of bias, such as maintaining confidentiality of any interim data.

Following the first IDMC review, a Sponsor Executive Committee (SEC) was formed consisting of Nektar's Chief Medical Officer, Head of Data Science and Systems, and Head of Regulatory Affairs, none of whom are directly involved in study conduct. In addition to the Medical Monitor's routine review of safety, the SEC will formally review safety at 6-month intervals.

10.0 PHARMACOKINETIC, PHARMACODYNAMIC, AND BIOMARKER ANALYSIS

Biomarker analyses described in this section may be summarized in separate report(s).

10.1 Pharmacokinetic Analysis

The pharmacokinetic analysis set (PKAS) will consist of 4 different analyses and will be summarized by the number and percentage of patients in each analysis set. The PKAS includes all patients who received at least 1 dose of NKTR-214 and at least 1 measurable concentration of:

- NKTR-214-RC PKAS: NKTR-214-RC
- NKTR-214-AC PKAS: NKTR-214-AC
- Total-PEG PKAS: Total-PEG
- Nivolumab PKAS: Nivolumab

Listings for blood collection dates, times and concentrations will be generated by patient for each analyte. Sampling time deviations will be computed as differences between scheduled (nominal) and actual sampling times and expressed in hours and as a percentage of the nominal time.

Observed plasma NKTR-214-RC, NKTR-214-AC, and Total-PEG, and serum nivolumab concentrations at each nominal PK sampling time will be listed by patient and tabulated for each analyte using descriptive statistics, including but not limited to n (observed), n (non-zero), arithmetic mean, standard deviation (SD), standard error of the mean (SE), arithmetic coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum.

Cycle 1 PK parameters for NKTR-214-RC, NKTR-214-AC and Total-PEG will be derived by Phoenix WinNonlin (version 8.3 or higher) based on noncompartmental methods. PK parameters are listed in Section 5.3.2. Linear up/log-down noncompartmental methods will be used to estimate AUC. The predose concentration of Cycle 2 may be duplicated as the last time time point of Cycle 1 for the calculation of PK parameters.

Noncompartmental analysis PK parameters will only be derived when all requirements, listed below (Table 10), are met. Where requirements are not met, PK parameter values will be noted as missing or not determinable:

Table 10: Noncompartmental Analysis Requirements

PK Parameter	Requirement
$t_{1/2}$, AUC_{inf}, CL, V_z	A minimum of 3 time points should be used for determining lambda_z, not including the Cmax time point. The span of the terminal phase must be at least 2 times the half-life for lambda_z to be determined. Where Rsq_adj < 0.75, lambda_z will not be determined If lambda_z is not determined then t1/2, AUCinf, CL, or Vz will not be reported.
AUC_{inf}	The extrapolated area should not contribute more than 20% to the total AUC_{inf} for the estimation of AUC_{inf}

Plasma NKTR-214-RC, NKTR-214-AC and Total-PEG PK parameterswill be listed by patient for each analyte for Cycle 1, and tabulated for each analyte for Cycle 1 using descriptive statistics, including but not limited to n (observed), geometric mean, mean, SE, SD, CV%, geometric CV%, median, minimum and maximum. Descriptive statistics for a PK parameter will be provided only if at least 60% of patients have a reportable PK parameter value. Descriptive statistics will not be performed if n<3 and summary tables will only include median, minimum, and maximum.

Mean (+ standard deviation) observed plasma NKTR-214-RC, NKTR-214-AC, and Total-PEG, concentrations versus nominal time plots will be generated on linear and semi-logarithmic scales for each analyte for Cycle 1 based on nominal sampling times. For serum nivolumab, mean (+ standard deviation) serum concentrations versus nominal time will be generated on linear scale by nominal sampling time. Nivolumab concentrations should not be connected by a line as all the samples are pre-dose concentrations from different cycles.

Rounding for the reporting of PK parameters will be to three significant digits. Percentages such as CV% presented in tables will be rounded to one decimal place. The same convention will be followed for descriptive statistics, except for n, which will be rounded to the whole value.

PK data obtained in this study may also be combined with data from other studies in the clinical development program to develop population PK models. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of bempegaldesleukin and/or nivolumab and to determine measures of individual exposure for nivolumab (such as single dose and steady state peak, trough and time averaged concentration) and for bempegaldesleukin (such as AUC, clearance, volume, half-life, Cmax, Cmin, and Cavg). Model predicted exposures may be used for exposure response analyses of selected efficacy and safety endpoints. If the analyses are conducted, the results of population PK and exposure response analyses will be reported separately.

10.1.1 Handling of Missing Values, BLQ, and Outliers

- NKTR-214-RC, NKTR-214-AC, and Total-PEG

  Missing concentration values will not be imputed. When summarizing concentrations, below the limit of quatification (BLQ) values will be considered as zero, and zero values will be excluded from the calculation of geometric means and CV% geometric mean, however, zero values will be included for all other summary statistics and the number of non-zero samples will be reported. Missing values for any PK parameters will not be imputed and will be handled as missing. Listings for concentrations values (except for pre-dose C1D1) will list these concentrations as <LLOQ.

  Samples with concentrations 5x higher than mean (mean + 5×SD) for all samples at that time will be considered outliers and not included in analyses and summary statistics and plots. The reason for not using selected data will be presented and discussed in the clinical study report (CSR).

  When calculating PK parameters, all Cycle 1 pre-dose concentrations that are BLQ will be set to 0; all other concentrations that are BLQ will be set to missing.

  Cycle 1 pre-dose concentration > 50% of Cycle 1 C_{max} will be excluded from concentration statistics and individual patient PK parameter calculation. Cycle 1 PK parameters for this subject may also be excluded from summary tables.

- Nivolumab

  When summarizing concentration values, BLQ values (except for pre-dose C1D1) will be imputed as LLOQ/2. Listings for concentrations values (except for pre-dose C1D1) will list these concentrations as <LLOQ. Pre-dose C1D1 BLQ values will be set to zero, and zero values will be excluded from the calculation of geometric means and CV% geometric mean, however, zero values will be included for all other summary statistics and the number of non-zero concentrations will be reported for pre-dose C1D1.

10.2 Blood Biomarker/Pharmacodynamic Analysis

Observed plasma sCD25 and cytokine concentrations, and fold change from baseline at each nominal sampling time and maximum fold change and time of maximum fold change will be listed by patient and tabulated for each analyte using descriptive statistics, including but not limited to n (number of non-missing data), arithmetic mean, SD, SE, arithmetic CV%, geometric mean, geometric CV%, median, 25^{th} and 75^{th} percentiles, minimum, and maximum.

For sCD25, all Cycle 1 pre-dose concentrations that are BLQ will be set to 0,all other concentrations that are BLQ will considered missing. Zero values will be excluded from the calculation of geometric means and CV% geometric mean. Missing concentration values will not be included in the descriptive statistics.

For cytokine, all BLQ values will be set to the lower limit of quantification (LLoQ).

Plot of mean (+SE) plasma sCD25, and cytokine concentrations versus nominal time will be generated for each analyte for baseline and Cycle 1 (including pre-dose Cycle 2, which will be set to Day 22). Fold change from baseline plots will also be generated. Baseline is the last observation prior to first dose within 2 weeks (or 14 days).

Plot of mean (+SE) cytokine concentrations and its fold change from baseline will be generated for baseline and all cycles.

Absolute eosinophil count, absolute lymphocyte count and their fold change from baseline will be summarized with descriptive statistics: n (number of non-missing data), arithmetic mean, SD, SE, CV%, median, 25th and 75th percentiles, minimum, and maximum.

Plot of mean (+SE) absolute lymphocyte counts and absolute eosinophil counts versus nominal time will be generated for baseline and Cycle 1 (including pre-dose Cycle 2, which will be set to Day 22). Fold change from baseline plots will also be generated. Baseline is the last observation prior to first dose within 2 weeks (or 14 days).

Plot of mean (+SE) eosinohpil trough count concentrations and its fold change from baseline will be generated for baseline and all cycles.

Rounding for the reporting of parameters will be to 3 significant digits. Percentages presented in tables such as CV% will be rounded to one decimal place. The same convention will be followed for descriptive statistics, except for n, which will be rounded to the whole value. Descriptive statistics will not be performed if $n < 3$ and summary tables will only include median, minimum, and maximum.

10.4 Concordance analysis

For all the available baseline tumor biopsies collected from both screen failure and treated patients, if applicable, the concordance analysis between 28-8 pharmDx and 22C3 pharmDx for evaluating PD-L1 status will be performed with summary agreement statistics including but not limited to overall percentage agreement (OPA), positive percent agreement (PPA), negative percent agreement (NPA), Lin's concordance correlation coefficient, and Cohen's K score. Additionally, the percentage of patients with CPS<10 by 28-8 and the percentage by 22C3 will be reported.

11.0 DOCUMENT HISTORY

Version Number	Author(s)	Description
1.0	[redacted]	Initial Version
2.0	[redacted]	• Section 2.0: add a statement for the event of a synoptic CSR resulting from negative primary analysis readout, in which only key efficacy and safety analyses described in this SAP will be performed to support the synoptic CSR. • Section 6.3: add the definition of NKTR-214, Nivolumab or GemCarbo Treated Population. • Section 6.5: the following changes have been made: o For the definition of Duration of Response (DOR), delete the statement "*or their first dose date if they do not have any on-study tumor assessment*", as DOR is only performed for patients who had response and those patients must have on-study tumor assessment. o For the definition Progression-free Survival (PFS), add a statement "*or if they do not have baseline assessment*" for patients who will be censored on their first dose date. o For the definition of clinical benefit rate (CBR), change the number of days that requires an observation of SD to 35 days (instead of 56 days) from the first dose date. This is to be consistent with Bioclinica Independent Review Charter for PIVOT-10 study. • Section 7.1: add the summary of descriptive statistics for the study treatment duration, and descriptive statistics for time to NKTR-214 discontinuation for patients who discontinued NKTR-214, into the disposition summary. • Section 7.2: add the categories and subcategories of important protocol deviations. • Section 7.3: the following changes have been made: o Add "*weight*" into the demographic summary. o Revise the geographic region with US/Canada, Europe, Rest of World, to be consistent with efficacy subgroup analysis by region in Section 7.5.4 and safety subgroup analysis by region in Section 7.8.11. o Add a statement "*Target lesions (Investigator and BICR Assessments at Baseline): presence of target lesions, site of target lesion, sum of reference diameter of target lesion*" and delete the statement "*Tumor burden at baseline per BICR and per investigator (<= 1st Tertile, > 1st Tertile to <= 2nd Tertile, >2nd Tertile).*" o Move "*metastases location (lymph node only, visceral), liver metastases*" into subsection 7.3.1. o In subsection 7.3.2, add a statement "*Treatment given in the non-muscle invasive setting, such as BCG vaccine or mitomycin is not considered treatment in the advanced setting. Also, patients who have received*

		neoadjuvant or adjuvant treatment are eligible as long as their disease did not relapse within 12 months from the last dose of treatment", and Clarify how we are summarizing the prior therapies as the statement below: "*The number and percent of patients who received prior therapy will be summarized. The number and percentage of patients who received cisplatin-containing, carboplatin-containing, gemcitabine-containing, or intravesical treatment will be calculated for the Treated Population. The number and percent of patients who received the setting of adjuvant, neoadjuvant, metastatic (if any) and locally recurrent regimens for locally recurrent and metastatic disease will be calculated for the Treated Population. Duration of prior therapy will be summarized descriptively. If a patient received multiple treatments of a therapy, the sum of duration will be calculated*." • Section 7.4: The following changes have been made: o In subsection 7.4.1, "*CYP inhibitors*" has been replaced by the term "*CYP substrates*". o In subsection 7.4.2, remove the concomitant surgery. o In subsection 7.4.3, remove the subsequent radiotherapy and subsequent surgery. o Add a subsection 7.4.4 for summary of immune-modulating concomitant mediations. o In subsection 7.4.5: (a) Delete summary of "*length of delay*" for patients who had dose delay. (b) Delete "*the number of patients with at least one IV infusion rate reduction and the reason for reduction*" as there is no such data collected. (c) Delete the redundant statements for time to and the reason of the first NKTR-214 dose reduction, the first dose interruption as they were stated in the bullets above. (d) In the last paragraph of subsection 7.4.5, change the term "*time to treatment discontinuation*" as "*time to study regimen discontinuation*", add the specific definitions for "*Time to study regimen discontinuation*" and "*Time to NKTR-214 treatment discontinuation*". • In section 7.5: The following changes have been made: o In subsection 7.5.1, add the following statements: "*The number and percentage of patients in each category of BOR per BICR (confirmed complete response [CR], confirmed partial response [PR], stable disease [SD], progressive disease [PD], or not evaluable [NE]) will be presented. The complete response rate and the partial response rate and their 95% CIs will also be presented*." o In subsection 7.5.2.1, delete the redundant statement: "*The complete response rate per BICR will be summarized similarly to ORR.*" o In subsection 7.5.3.1, in table 3 and table 4, add a censoring rule for the situation of "*no on study tumor assessment and no death*", and the censoring date is "*first dose date*". o Add a subsection 7.5.3.3 for concordance between BICR and Investigator Assessment of Progression.

		○ Add a subsection of 7.5.3.5 for current status of PFS and OS Follow-up. ○ In section 7.5.3.8, delete the sensitivity analysis for DOR. ○ In subsection 7.5.4, add subgroup analysis for "*Metastases location (lymph node only, visceral disease)*" and "*Liver metastases (present, absent)*" • Section 7.7: The following changes have been made: ○ In subsection 7.7.1, removed sample level ADA analysis by analyte and by visit. Clarified that samples confirmed to be positive for anti-NKTR-214/anti-PEG, anti-IL-2 antibodies will be tested for neutralizing activity for IL-2 using a validated cell-based assay. Anti-nivolumab antibodies positive samples will also be tested for neutralizing activity for nivolumab using a validated cell-based assay. ○ Add a subsection 7.7.2 for the details of the safety evaluation of ADA. Clarified that infusion related reaction events that start after study drug administration on the same day or next day will be included. Clarified that pre-dose NKTR-214 RC and pre-dose NKTR-214 AC concentrations will be summarized by ADA status. • Section 7.8.1: The following changes have been made: ○ In subsection 7.8.1.1, add a statement to clarify the definition of NKTR-214 related TEAE, and delete the statement "*The sorting will be done based on the 'Any Grade' column of the experimental arm when arms are presented side-by-side*" as it is not applicable in this study. ○ In subsection 7.8.1.2, rename to "*select adverse events*" to be "*select immune-related adverse events (irAEs)*", add details statements for the identification of select irAEs. ○ In subsection 7.8.1.3, rename to "*other events of special interest (OEOSI)*" to be "*other immune-related adverse event of special interest (OirAESI)*". ○ In subsection 7.8.1.4, add some statements to clarify the IMAEs. ○ Section 7.8.2: in subsection 7.8.2.1, remove the summary of AEs leading to death excluding progression terms, and add NKTR-214-related AEs leading to death, any drug-related AEs leading to death • Section 7.8.3: add the summary for NKTR-214 related SAEs. • Section 7.8.4: add the summary of NKTR-214 related AEs leading to discontinuation of bempegaldesleukin. • Section 7.8.5: remove the summary of AEs leading to dose delay, and this will only be listed; add the summary of NKTR-214 related AEs leading to dose reduction of bempegaldesleukin. • Section 7.8.6: add the following NKTR-214-related TEAE summaries: ○ NKTR-214-related TEAEs ○ Grade 3 or above NKTR-214-related TEAE ○ Serious NKTR-214-related TEAE ○ NKTR-214-related TEAE (using an extended treatment-emergent period)

		• Section 7.8.8: Clarified that IMAEs will be summarized using the extended treatment-emergent period for each immune-mediated category. Re-challenge analysis is removed. • Section 7.8.10: The following changes have been made: o In subsection 7.8.10.1, time to resolution analysis for ICE is removed, and exposure adjusted analysis for ICE is removed. o In subsection 7.8.10.2, time to resolution analysis for OSO is removed • Section 7.10: Table 9 (Criteria for Clinically Notable Vital Sign Abnormalities) is updated. • Section 8.2: The analysis on COVID-19 impacts on efficacy results may be performed if needed • Section 11: Document History section is added.

12.0 REFERENCES

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APPENDIX 1: TIME-TO ONSET AND TIME-TO RESOLUTION DEFINITION AND CONVENTIONS FOR SELECT IMMUNE-RELATED ADVERSE EVENTS, IMMUNE-MEDIATED ADVERSE EVENTS AND EVENTS OF SPECIAL INTEREST

Time-to onset definition

Time-to onset of AE (any grade) for a specific category is defined as the time between the day of the first dose of study treatment and the onset date of the earliest AE (of any grade) in this category.

The time-to onset of AE (Grade 3-5) for a specific category is defined similarly with an onset date corresponding to a Grade 3-5 AE.

Time-to onset of drug-related AE (any grade or Grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

Time-to onset for a specific subcategory is defined similarly but restricted to event of this subcategory.

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous AEs within a specific category or subcategory will be collapsed into what will be termed “clustered” AEs. For example, if a subject (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered AE from 1st to 12th January. Table 11 is summarizing key derivation steps for each type of clustered AEs.

Time-to resolution of AE (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered AEs experienced by the subject in this category per adverse event criteria category. Events which worsened into grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AE is considered as unresolved, the resolution date will be censored to the last known alive date. Improvement to the grade at baseline implies that all different events in the clustered adverse event should at least have improved to the corresponding (i.e. with same preferred term) baseline grade. This measure is defined only for patients who experienced at least one AE in the specific category.

The time-to resolution of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to resolution of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

The time-to resolution of AE (any grade or grade 3-5, drug-related or all) where immune-modulating medication was initiated is defined similarly. For data presentation not restricted to IMAE, the additional condition that the subject started an immune-modulating medication during the longest AE resolution period will be applied.

Time-to resolution for a specific subcategory is defined similarly but restricted to event of this subcategory.

Table 11: Derivation of Clustered AE

Type of clustered AE	Derivation
Any grade	Collapse any TEAE from the same category
Drug-related of any grade	Collapse any drug-related TEAE from the same category
Grade 3-5	Collapse any TEAE from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 records (if no grade 3-5 record, clustered TEAE is excluded)
Drug-related of Grade 3-5	Collapse any drug-related TEAE from the same category Resolution will be based on the onset date of the earliest Grade 3-5 record (if no Grade 3-5 record, clustered TEAE is excluded)

The algorithm for collapsing adverse event records is using the following conventions:

For each subject and specified category, the corresponding adverse event records will be collapsed when:

1) Multiple adverse event records have the same onset date.
2) The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
3) The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).