Nektar Therapeutics

STATISTICAL ANALYSIS PLAN

A PHASE 1/2, OPEN-LABEL, MULTICENTER STUDY OF THE COMBINATION OF NKTR-214 AND NIVOLUMAB OR THE COMBINATION OF NKTR-214, NIVOLUMAB, AND OTHER ANTI-CANCER THERAPIES IN PATIENTS WITH SELECT LOCALLY ADVANCED OR METASTATIC SOLID TUMOR MALIGNANCIES

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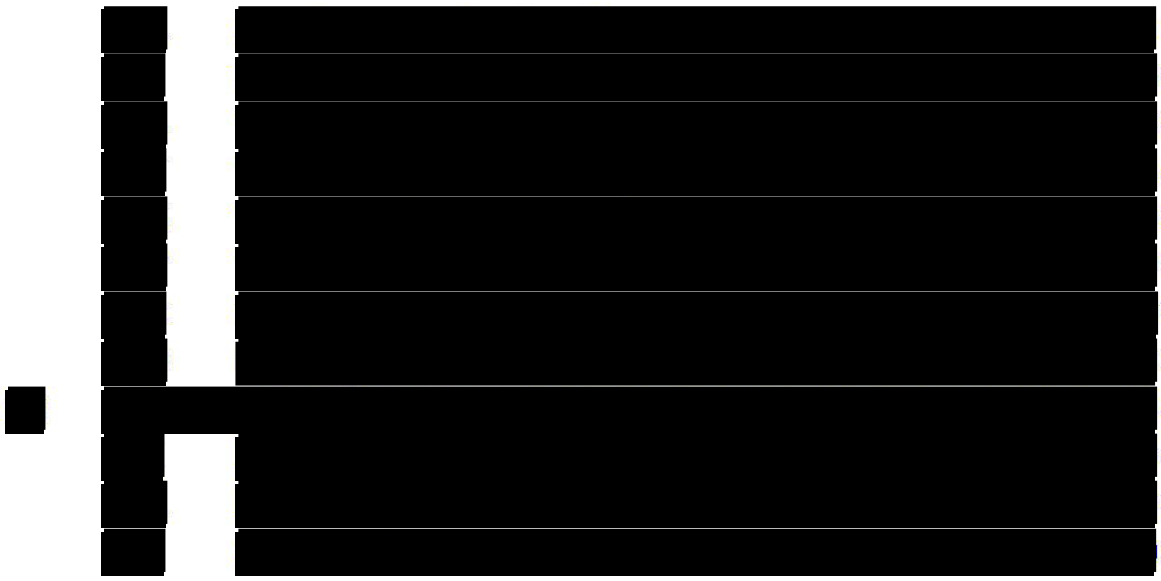

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LIST OF ABBREVIATIONS AND ACRONYMS

Acronym/Abbreviation	Definition
1L	first line
2L	second line
3L	third line
ADA	anti-drug antibody
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
ATC	anatomical therapeutic chemical
AUC	area under the curve
BAS	biomarker analysis set
BL	Baseline
BLQ	below the limit of quantification
BMI	body mass index
BOR	best overall response
BRAF	proto-oncogene B-Raf
BSA	body surface area
C1D1, C2D1, C3D1, etc.	Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, etc.
CBR	clinical benefit rate
cis	Cisplatin
CL	Clearance
C_{max}	maximum observed concentration/Maximum observed count
CR	complete response
CRC	colorectal carcinoma
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated protein 4
CV	coefficient of variation
CVA	cerebrovascular accident
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECLA	electrochemiluminescence assays
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor

Acronym/Abbreviation	Definition
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
FNR	false-negative rate
FPR	false-positive rate
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HR	hormone receptor
ICH	International Council for Harmonisation
IL-2	interleukin-2
imAE	immune-mediated adverse event
I-O	immuno-oncology
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IRT	interactive response technology
IV	Intravenous
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Melanoma
mg	Milligram
MSI	microsatellite instability
MTD	maximum tolerated dose
N1	sample size at stage 1
N2	sample size at stage 2
NCA	noncompartmental analysis
NCI	National Cancer Institute
NK	natural killer
NKTR-214-AC	NKTR-214 active cytokine metabolites
NKTR-214-RC	NKTR-214 related cytokines
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PEG	polyethylene glycol
PFS	progression-free survival

Acronym/Abbreviation	Definition
PK	pharmacokinetic/s
PKAS	pharmacokinetic analysis set
PR	partial response
PT	preferred term
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
q6w	every 6 weeks
QTcF	Fridericia's corrected QT interval
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
S1	futility boundary at stage 1
S2	futility boundary at stage 2
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SCLC	small-cell lung cancer
SOC	system organ class
T1	efficacy boundary at stage 1
T2	efficacy boundary at stage 2
$T_{1/2}$	terminal elimination phase half-life
T3	Triiodothyronine
T4	free thyroxine
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
TIA	transient ischemic attack
T_{max}	time to maximum concentration/Time to reach maximum count
TNBC	triple-negative breast cancer
TTR	time to response
WHODDE	World Health Organization Drug Dictionary Enhanced

1.0 INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical methods to be implemented during the analyses of the data collected within the scope of Nektar Therapeutics Protocol 16-214-02 [A Phase 1/2, Open-label, Multicenter Study of the Combination of NKTR-214 and Nivolumab or the Combination of NKTR-214, Nivolumab, and Other Anti-Cancer Therapies in Patients with Select Locally Advanced or Metastatic Solid Tumor Malignancies] Amendment 7.0 dated 11 February 2020. The purpose of this SAP is to provide details on the planned statistical analyses of the efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity data. Any deviations from the SAP will be documented in the clinical study report (CSR).

This Phase 1/2 study is conducted in accordance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements. This SAP was written with consideration of the recommendations outlined in the International Council for Harmonization (ICH) E9 Guideline entitled "Statistical Principles for Clinical Trials".

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

- To evaluate the safety and tolerability, and define the maximum tolerated dose (MTD) and/or recommend Phase 2 dose (RP2D) of NKTR-214 in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies
- To evaluate the efficacy of NKTR-214 in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies by assessing the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) at the RP2D

2.2 Secondary Objective

- To evaluate the efficacy of NKTR-214 in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies by assessing overall survival (OS), progression-free survival (PFS), clinical benefit rate (CBR), and duration of response (DOR)

[redacted]

3.0 STUDY DESIGN AND PLAN

3.1 Study Design

This is a Phase 1/2, open-label, multicenter, dose escalation, and dose expansion study of NKTR-214 in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies in patients with locally advanced or metastatic solid tumor malignancies who have measurable disease including locally advanced or metastatic melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), urothelial carcinoma, triple-negative breast cancer (TNBC), hormone-receptor positive breast cancer, gastric cancer, colorectal cancer (CRC), or small cell lung cancer (SCLC). The study design consists of four parts: dose escalation (Part 1) for the combination of NKTR-214 and nivolumab, dose expansion (Part 2) for the combination of NKTR-214 and nivolumab with/without other anti-cancer therapies, and dose escalation or schedule finding (Part 3) and dose expansion (Part 4) for NKTR-214 in combination with nivolumab and ipilimumab.

The study is divided into a Screening period, Treatment period, End of Treatment period, and Long-Term Follow-up period. Patients will receive treatment depending on the study period and the cohort into which they are enrolled. Cohorts are classified by indication and further sub-classified by line of therapy and type of most recent anti-cancer treatment received (See Figure 1 and Figure 2 in Section 3.4 and Appendix 2). Treatment cycle is defined by the frequency of NKTR-214 administration.

3.2 Study Population

Adults aged 18 years and older with select locally advanced or metastatic solid tumor malignancies who have measurable disease with melanoma, RCC, NSCLC, urothelial carcinoma, TNBC, hormone-receptor positive breast cancer, gastric cancer, CRC, or SCLC.

3.3 Study Medications

In the doublet dose escalation phase (i.e., Part 1 of the study), the 3 + 3 design was used to investigate NKTR-214 at a dose level 0.006 mg/kg q2w or q3w and 0.009 mg/kg q3w in combination with nivolumab at a dose level of 240 mg q2w or 360 mg q3w in various solid tumor malignancies. Other dose levels and dosing frequencies of NKTR-214 may also have been evaluated.

In the triplet dose escalation phase (i.e., Part 3 of the study), NKTR-214 0.006 mg/kg q3w was evaluated in combination with nivolumab and ipilimumab at 3 different dosing schedules. Additional patients may have been enrolled into the dose escalation cohorts in Part 1 or Part 3.

In the dose expansion phases, the doublet and triplet regimens (i.e., Part 2 and Part 4 of the study, respectively) were evaluated in various solid tumor malignancies to further evaluate the safety and

efficacy of the treatment combinations. In Part 2, NKTR-214 0.006 mg/kg q3w and nivolumab 360mg q3w was administered in combination with other anti-cancer therapies for selected solid tumor malignancies. In Part 4, NKTR-214 0.006 mg/kg q3w was evaluated in combination with nivolumab and ipilimumab at the 3 different dosing schedules from Part 3.

Each patient's NKTR-214 dose was determined by the NKTR-214 dose escalation scheme and the patient's weight in kilograms, which was determined before the start of each cycle. Depending on institutional guidelines/preferences, if the patient's weight was within 10% of the Cycle 1 Day 1 weight, the study drug doses may not have been recalculated. NKTR-214 was administered intravenously (IV).

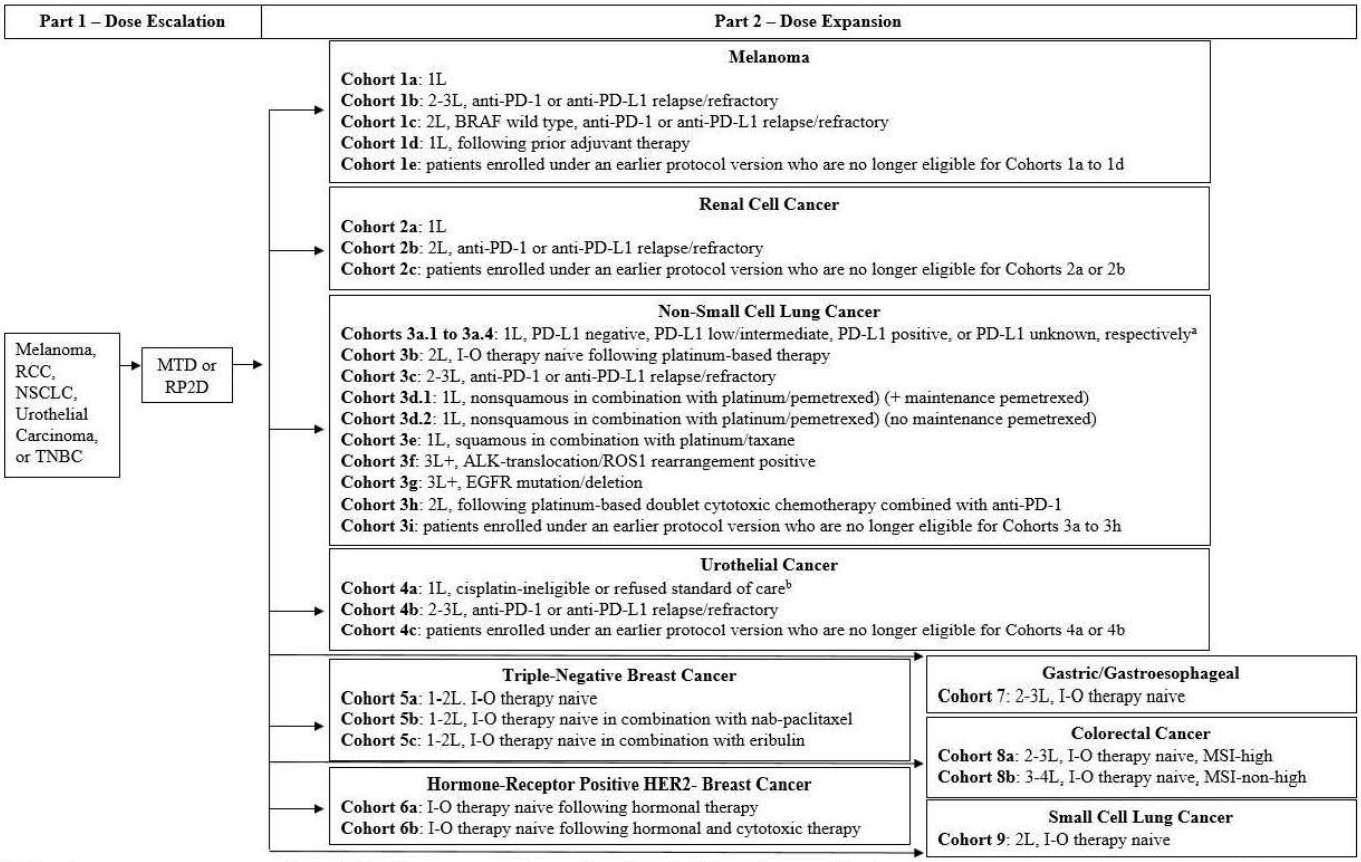
NKTR-214 was administered before nivolumab, ipilimumab, or other anti-cancer therapy.

In case of NKTR-214 drug-related toxicities requiring dose delays, reductions or discontinuation, nivolumab or ipilimumab could continue in the absence of nivolumab-related or ipilimumab-related toxicities. If the NKTR-214 dose was reduced to 0.003 mg/kg, the dose remained at this level throughout the remainder of the study. Dose delays were also permitted for nivolumab and ipilimumab, but dose reductions were not permitted.

Patients were treated until disease progression, death, unacceptable toxicity, symptomatic deterioration, achievement of maximal response or up to 2 years to therapy, the Investigator's decision to discontinue treatment, patient decision to discontinue treatment or withdraw consent, the patient was lost to follow-up, or Nektar Therapeutics decision to terminate the trial. Patients with progressive disease (PD) per RECIST 1.1, but with otherwise stable or improved performance and clinical status, may have continued treatment in the event that the Investigator perceived benefit provided the patients met the protocol-defined criteria.

3.4 Study Schematic

Figure 1: Study Schematic for Part 1 Dose Escalation and Part 2 Dose Expansion

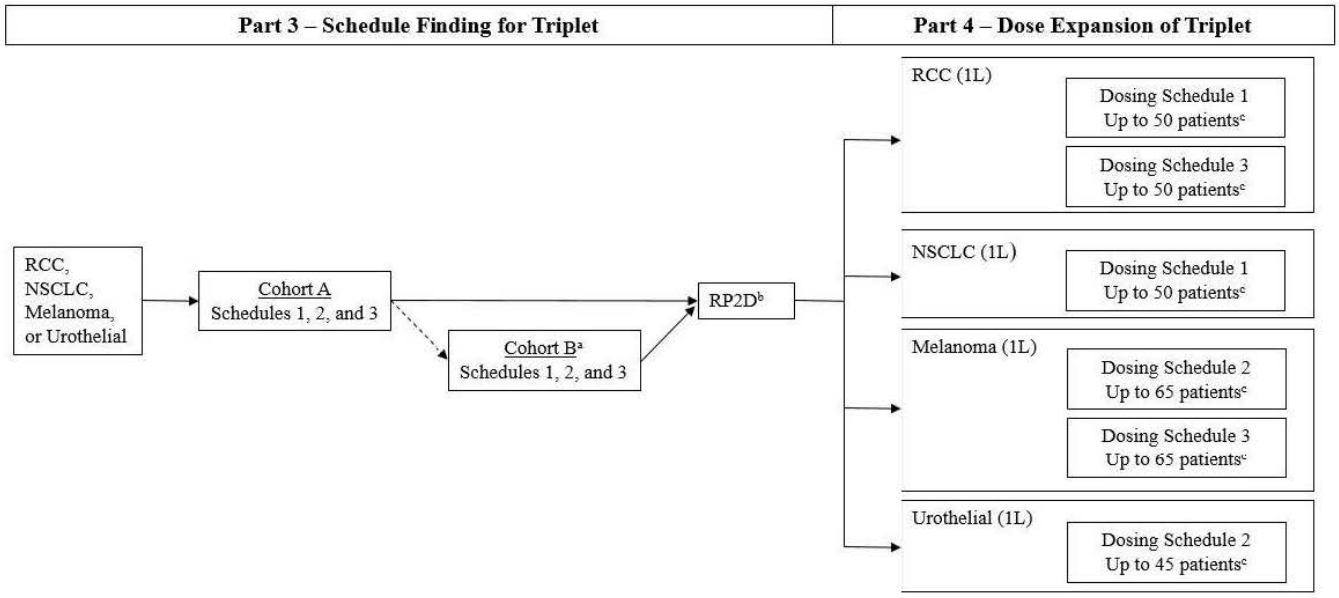


HR+ = hormone-receptor positive; I-O = immuno-oncology; L = line; MSI = microsatellite instability; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; RP2D = recommended Phase 2 dose; SOC = standard of care; TNBC = triple-negative breast cancer

a. Up to 20 efficacy-evaluable NSCLC patients will be enrolled in each cohort of PD-L1 negative, PD-L1 low/intermediate, or PD-L1 positive. Patients enrolled in Cohort 3a who do not have a PD-L1 status assessed by central testing will be assigned to Cohort 3a.4.

b. Up to 20 urothelial carcinoma 1L patients who are cisplatin-ineligible and (for countries other than Italy) up to 20 patients who choose to forego standard of care.

Figure 2: Study Schematic for Triplet Part 3 Schedule Finding and Part 4 Dose Expansion



a. If administration of all 3 study drugs on the same day in Cohort A meets criteria listed in Section 5.3.5 of the study protocol, Cohort B may be initiated, where ipilimumab will be staggered to be administered at a later cycle (e.g., Cycle•3 Day•1)

b. In Part 3, the RP2Ds will be established for each of the 3 dosing schedules (it may be necessary for a separate RP2D to be established for patients with melanoma and urothelial cancers, if the tolerability is different between these 2 groups).

c. Includes patients from both Part 3 and Part 4.

4.0 STUDY ENDPOINTS

4.1 Primary Endpoints

In Part 1 and Part 3, the primary endpoint is the incidence of dose limiting toxicity (DLT) during the DLT evaluation window.

For efficacy, the primary endpoint is ORR per RECIST 1.1 at RP2D.

4.2 Secondary Endpoints

For safety, the secondary endpoints include:

- Incidence of adverse events (AEs)
- Incidence of serious adverse events (SAEs)
- Incidence of Grade 3 or above adverse events (AEs)
- Incidence of clinically significant laboratory abnormalities, vital signs, electrocardiography (ECG), and physical exams.

For efficacy at RP2D, the secondary endpoints include:

- Best overall response (BOR) using RECIST 1.1.
- Time to response (TTR) using RECIST 1.1
- DOR using RECIST 1.1
- CBR using RECIST 1.1
- PFS using RECIST 1.1
- OS

[redacted]

5.0 STATISTICAL CONSIDERATIONS

5.1 General Analysis Considerations and Definitions

The statistical analyses will be reported using summary tables, figures, and data listings. Data listings will be presented by treatment group and patient identification number. Unless otherwise specified, data collected during the Part 1 will be presented by dose and overall for Part 1 patients. Data collected from patients who are dosed at the RP2D level in Part 1 and Part 2 will be combined and presented by tumor indication and cohort (see Appendix 2 for more details). Data collected from Parts 3 and 4, dose finding and expansion phases for the triplet combination respectively, will be combined and presented by tumor indication and dosing schedule.

Because of the nature of basket trial design and the evolving landscape, some indications have been further classified and/or re-classified into sub-indications through protocol amendments. Therefore, patients to be reported in the same cohort may have different diagnoses/sub-diagnoses in the cancer history CRF form depending on the protocol version and study phase under which they are enrolled. For statistical analysis purposes, the final classification of cohorts is provided in the Appendix 2.

Summary statistics for continuous variables will include the mean, standard deviation, median, minimum, and maximum. The mean will be presented to one decimal place beyond which the data were captured. The standard deviation will be presented to two decimal places beyond which the data were captured. The minimum and maximum will be presented to the precision with which the data were captured.

Categorical variables will be presented by frequency counts and percentages. A row or column denoted 'Missing' will be included in count tabulations where necessary to account for dropouts and missing values. Percentages will be rounded to one decimal place and the percent will be suppressed when the count is zero. The denominator will be the number of patients in that dose cohort/tumor type within the population of interest unless otherwise noted.

Time-to-event variables will be analyzed using the Kaplan-Meier (KM) method. The number and percentage of patients with events or censored will be presented. The KM estimates for quartiles (i.e., 25%, median, and 75%) and 95% confidence interval using log(-log(s(t))) transformation with Greenwood's formula for variance for the median will be presented. All time to event variables will be plotted using the KM method with censoring and risk set displayed.

All data will be listed, including data collected from the electronic case report form (eCRF) and derived for statistical analysis. Unless otherwise specified, incomplete data will not be imputed in the listing.

No formal statistical hypothesis testing is planned. All statistical analyses will be carried out using SAS® version 9.4 or later (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

5.2 Determination of Sample Size

During Part 1, cohorts of at least 3 patients were treated at each dose level. Additional patients were added to each dose cohort based on the scheme and rules outlined in the protocol or Sponsor determination of the need for additional data to further evaluate the benefit/risk profile. Approximately 50 patients were to be enrolled into the Part 1 dose escalation phase.

During Part 3, cohorts of at least 6 patients were enrolled into each of the 3 concurrent dosing schedules as listed in the protocol. Additional patients were added to each dose schedule based on the scheme and rules outlined in the protocol or the Sponsor's determination of the need for additional data to further evaluate the benefit/risk profile. Based on emerging safety and biomarker data from the concurrent dosing schedules, patients may have enrolled into staggered dosing, where ipilimumab was staggered to be administered at a later cycle (e.g., Cycle 3 Day 1). Approximately 36 patients were to be enrolled into the Part 3 dose-escalation phase.

During Parts 2 and 4, the sample size was calculated based on the target ORR relative to historic response rate. The Fleming 2-stage design (Fleming, 1982) framework was used as a guide. The total sample size (including patients dosed at the RP2D from the dose escalation phase of Part 1) for each expansion cohort was calculated using a normal approximation to provide a reasonable false-positive rate (FPR < 10%) and false-negative rate (FNR < 10%) based on assumptions of true (target) and historic ORR for each indication Table 1 and Table 2). The historic and target response rate assumptions may have changed over time and may have been adjusted at the time the response data from this study were available. The 2-stage design provided an option to stop early for futility as well as allowing an early start for Phase 3 preparation if a strong antitumor activity signal was observed. However, the final decision was to be based on the totality of overall treatment effect for multiple study endpoints and their associations with the tumor response rate. Enrollment may have continued into Part 2 while the planned number of patients for Part 1 were followed for tumor assessments. There was to be no stopping of enrollment to a tumor cohort for efficacy, although early planning for the next stage of clinical development may have been initiated.

Table 1: True (Target) and Historic Objective Response Rate for Each Indication in Part 2

Cohort[a]	Indication	Objective Response Rate (%)		Sample Size[b]			Futility		Efficacy		Reference for Historical ORR Assumption
		Historical	Target	N1	N2	Total	S1	S2	T1	T2	
1a	MEL 1L	40	65	13	15	28	≤ 5	≤ 14	≥ 10	≥ 15	Robert, 2015
1b	MEL 2-3L, I-O relapse/ refractory	10	30	15	11	26	≤ 1	≤ 5	≥ 4	≥ 6	Unmet medical need
1c	MEL 2L BRAF wild type I-O relapse/ refractory	10	30	15	11	26	≤ 1	≤ 5	≥ 4	≥ 6	Unmet medical need
1d	MEL 1L following prior adjuvant therapy	10	30	16	12	28	≤ 1	≤ 5	≥ 4	≥ 6	Nomura, 2017; Weber, 2013
2a	RCC 1L	25	50	11	15	26	≤ 2	≤ 9	≥ 6	≥ 10	Topalian, 2012
2b	RCC 2-3L, I-O relapse/ refractory	5	25	15	11	26	≤ 0	≤ 3	≥ 3	≥ 4	Unmet medical need
3a	NSCLC regardless of PD-L1 expression	23	45	16	18	34	≤3	≤11	≥7	≥12	Garon 2015; Gettinger 2016; Carbone, 2017
3a.1	NSCLC 1L PD-L1 < 1%	8	30	12	8	20	≤ 0	≤ 3	≥ 3	≥ 4	Garon, 2015; Carbone, 2017
3a.2	NSCLC 1L PD-L1 ≥ 1%-< 50%	14	40	8	10	18	≤ 0	≤ 4	≥ 4	≥ 5	
3a.3	NSCLC 1L PD-L1 ≥ 50%	25	55	11	9	20	≤ 3	≤ 7	≥ 6	≥ 8	
3b	NSCLC 2L, I-O therapy naive following platinum-based therapy	20	40	20	16	36	≤ 4	≤ 10	≥ 8	≥ 11	Brahmer, 2015
3c	NSCLC 2L, I-O relapse/refractory	5	20	12	25	37	≤0	≤3	≥3	≥4	Unmet medical need
3d.1	NSCLC, 1L nonsquamous in combination with platinum/pemetrexed (+ maintenance pemetrexed)	45	66	20	19	39	≤ 9	≤ 21	≥ 14	≥ 22	Gandhi, 2018

Table 1: True (Target) and Historic Objective Response Rate for Each Indication in Part 2 (Contd)

Cohort[a]	Indication	Objective Response Rate (%)		Sample Size[b]			Futility		Efficacy		Reference for Historical ORR Assumption
		Historical	Target	N1	N2	Total	S1	S2	T1	T2	
3d.2	NSCLC, 1L nonsquamous (no maintenance pemetrexed)	45	66	20	19	39	≤ 9	≤ 21	≥ 14	≥ 22	Gandhi, 2018
3e	NSCLC 1L squamous in combination with platinum/taxane	20	40	20	16	36	≤ 4	≤ 10	≥ 8	≥ 11	Rizvi, 2016
3f	3L+ NSCLC ALK-translocation/ ROS1 rearrangement positive	5	20	12	25	37	≤0	≤3	≥3	≥4	Unmet medical need
3g	3L+ NSCLC, EGFR mutation/deletion	5	20	12	25	37	≤0	≤3	≥3	≥4	Unmet medical need
4a	Urothelial 1L Cis-ineligible	16	45	10	8	18	≤1	≤5	≥4	≥6	Balar, 2017
	Urothelial 1L (refused standard of care)	16	45	10	8	18	≤1	≤5	≥4	≥6	
4b	Urothelial 2-3L, I-O relapse/ refractory	5	25	13	7	20	0	≤2	≥3	≥3	Patel, 2018
5a	TNBC 1-2L, I-O therapy naïve	10	26	21	17	38	≤ 1	≤ 6	≥ 5	≥ 7	Schmid, 2017
5b	TNBC 1-2L, I-O therapy naive + nab-paclitaxel	24	45	20	18	38	≤ 5	≤ 12	≥ 9	≥ 13	Forero-Torres, 2015; Gradishar, 2005
5c	TNBC 1-2L, I-O therapy naive + eribulin	20	40	20	16	36	≤ 4	≤ 10	≥ 8	≥ 11	Kaufman, 2015; McIntyre, 2014
6a	HR+ breast cancer, I-O therapy naive following hormonal therapy	25 (cytotoxic chemo-therapy)	45	18	21	39	≤ 5	≤ 14	≥ 9	≥ 15	Harris, 2006; Twelves, 2014
		5% (for single agent CPI)	20	12	25	37	0	≤ 3	≤ 3	≥ 4	Rugo 2016; Dirix 2018

Table 1: True (Target) and Historic Objective Response Rate for Each Indication in Part 2 (Contd)

Cohort[a]	Indication	Objective Response Rate (%)		Sample Size[b]			Futility		Efficacy		Reference for Historical ORR Assumption
		Historical	Target	N1	N2	Total	S1	S2	T1	T2	
6b	HR+ breast cancer, I-O therapy naive following hormonal and cytotoxic therapy	20 (cytotoxic chemo-therapy)	40	20	16	36	≤ 4	≤ 10	≥ 8	≥ 11	Harris, 2006; Twelves, 2014
		5% (for single agent CPI)	20	12	25	37	0	≤ 3	≤ 3	≥ 4	Rugo 2016; Dirix 2018
7	Gastric carcinoma 2-3L, I-O therapy naïve	13	30	22	15	37	≤ 2	≤ 7	≥ 7	≥ 8	Kang, 2017
8a	CRC 2-3L, MSI-high, I-O therapy naïve	30	50	26	13	39	≤ 7	≤ 15	≥ 13	≥ 16	Overman, 2017
8b	CRC 3-4L, MSI-non-high, I-O therapy naïve	5	20	12	25	37	≤ 0	≤ 3	≥ 3	≥ 4	Le, 2015 (mismatch repair proficient)

BRAF = proto-oncogene B-Raf; cis = cisplatin; CPI = checkpoint inhibitor; CRC = colorectal carcinoma; EGFR = epidermal growth factor receptor; HR+ = hormone-receptor positive; I-O = immuno-oncology; L = line; MEL = melanoma; MSI = microsatellite instability; N1, N2 = sample size at stage 1, 2; NA = not available; ORR = objective response rate; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; S1, S2 = futility boundary at stage 1, 2; T1, T2 = efficacy boundary at stage 1, 2; TNBC = triple-negative breast cancer

a. Cohort 3h is not included in this table but is discussed separately in the following paragraph.

b. Total sample size for each expansion cohort is calculated using a normal approximation to provide a reasonable false-positive rate (FPR < 10%) and false-negative rate (FNR < 10%).

For efficacy assessment of Cohort 3h (patients with immuno-oncology relapsed-refractory NSCLC whose disease has progressed on combination therapy of anti-PD-1/anti-PD-L1 with cytotoxic chemotherapy), the historical comparator was single-agent docetaxel which showed 9% overall response rate in a second-line NSCLC population (Herbst, 2016). With this historical control rate as the null hypothesis, using a two-sided alpha of 0.05, 100 patients provided over 90% power to demonstrate statistical significance if the response rate of NKTR-214/nivolumab was 20% or more. If the observed response rate in this cohort was 18% or better, the lower bound of the 95% confidence interval would rule out a 10% response rate.

Two interim analyses were to be conducted in Cohort 3h to gate the trial progression based on the Response Evaluable Population. The first interim evaluation was to be conducted when 20 evaluable patients had been followed for 4 months or terminated from the study. If 3 or more responses are observed, the trial may have continued to the next stage. The second interim analysis was to be performed when 40 evaluable patients had been followed for 4 months or terminated from the study. If there were 6 or more responders, the trial may have continued to enroll approximately 100 patients. Enrollment was to continue without pause during the conduct of the interim analyses.

Approximately 936 patients were to be enrolled into Part 2. Additional patients may have been added to selected expansion cohorts to further evaluate the benefit/risk profile.

Approximately 36 patients were to be enrolled into Part 3.

Up to an additional 106 patients were to be enrolled into Part 4.

Table 2: True (Target) and Historic Objective Response Rate for Each Indication in Parts 3 and 4

	Objective Response Rate		Sample Size[a]			Futility		Efficacy	
Indication	Historical	Target	N1	N2	Total	S1	S2	T1	T2
RCC 1L	25	50	11	15	26	≤2	≤9	≥6	≥10
NSCLC 1L[b]	25	50	11	15	26	≤2	≤9	≥6	≥10
Melanoma 1L	40	65	13	15	28	≤5	≤14	≥10	≥15
Urothelial 1L	25	50	11	15	26	≤2	≤9	≥6	≥10

Abbreviations: L = line; N1, N2 = sample size at stage 1, 2; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; S1, S2 = futility boundary at stage 1, 2; T1, T2 = efficacy boundary at stage 1, 2

a. Total sample size for each cohort is calculated using a normal approximation to provide a reasonable FPR < 10% and FNR < 10%.

b. Total sample size for 1L NSCLC is based on the assumption that a mixed population of PD-L1 positive and negative patients will be enrolled. If unequal distribution of patients are enrolled, sample size may be modified accordingly.

5.3 Cohort Assignment

This is an open-label, non-randomized study. The patient, Investigator and Sponsor were not blinded to the patient's treatment. Patients were assigned via interactive response technology (IRT) to each cohort based on the Investigator's assessment during the Screening period, prior to enrollment. The Sponsor reviewed and identified any discrepancies with the Investigator's cohort assignment. Patients assigned to

the incorrect cohort were reclassified or remapped to the appropriate cohort by the Sponsor (Appendix 2).

Patients enrolled in Parts 1 and 3 who did not complete the DLT observation period for reasons other than a DLT were to be replaced to provide a sufficient number of patients to support the dose escalation decision. Patients enrolled in Parts 2 and 4 who did not meet all eligibility criteria were replaced.

5.4 Analysis Populations

All Enrolled Population: All patients enrolled into the study and assigned a patient identification number.

Safety Population: All patients who receive at least 1 dose (or partial dose) of study drug.

DLT Population:

Part 1: All Part 1 patients meeting either of the following two criteria:

1) Took study treatment and followed up at least through the DLT evaluation period depending on the dosing schedule listed below:
   a) For q2w dosing: patients received at least 2 cycles of study medication and stayed in the study for at least 28 days.
   b) For q3w dosing: patients received at least 1 cycle of study medication and stayed in the study for at least 21 days.

or

2) Discontinued from the study treatment due to DLT.

Part 3: All Part 3 patients meeting either of the following two criteria:

1) Patients received at least 1 cycle of study medication and stayed in the study for at least 21 days after first dose of ipilimumab.

or

2) Discontinued from the study treatment due to DLT.

Response Evaluable Population: Patients who have measurable disease (per RECIST 1.1) at baseline and also have at least 1 post-baseline assessment of tumor response prior to receiving new systemic anti-cancer therapy, surgical procedures or radiotherapy on target lesions.

Pharmacokinetic Population: All patients in the Safety Population who have sufficient concentration-time data to support computation of at least one PK parameter value.

Immunogenicity Population: All patients in the Safety Population with at least baseline and 1 post-baseline ADA assessment.

[redacted]

5.5 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 5.5.1 through 5.5.6.**

5.5.1 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

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

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

In order to calculate the duration of immune modulating medication for management of drug-related select AEs or 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.

5.5.2 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.

5.5.3 New Anti-Cancer Therapy

For new 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 new anti-cancer therapy is complete:
    - Minimum of (the last day of the month, end date of new anti-cancer therapy)
  - If the end date of new 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 new anti-cancer therapy is complete:
    - Maximum of (Minimum of (01 July + partial year, end date of new anti-cancer therapy), C1D1 + 1)
  - If the end date of new anticancer therapy is not complete:
    - Maximum of (01 July + partial year, C1D1 + 1).

5.5.4 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.

5.5.5 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 only 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.

5.5.6 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).

Handling of missing data for the efficacy analyses of PFS, OS, and DOR is described in Section 7.12.

No imputation of other missing data is planned.

6.0 ANALYTIC DEFINITIONS

6.1 General Definition

Age: due to regulatory restrictions, collection of complete date of birth data is not permitted at some sites. The age at screening will be collected via IRT, and will be used for analysis. No derivation will be performed.

Baseline: unless medically justified and documented, baseline is defined as the results collected at the last assessment on or before C1D1 date and time (last assessment on or before C1D1 date if time is not available).

Study day: there is no study day zero. Date of C1D1 is study day 1. For any events prior to C1D1, the study day is derived as date of event minus date of C1D1. For any events after C1D1, the study day is defined as date of event minus the date C1D1 plus 1.

Visceral disease: given the study will enroll patients across various tumor malignancies, there is no general definition for visceral disease. Visceral disease will be determined based on medical review for each specific tumor malignancy.

6.2 Baseline Characteristics

Body mass index (BMI) (kg/m^2) is defined as weight (kg)/ $height^2$ (m^2)

Body surface area (BSA) will be calculated using the Mosteller formula (Mosteller, 1987):

$$BSA\ (m^2) = \{ [\ height\ (cm) \times weight\ (kg)\ ]/3600\ \}^{1/2}$$

6.3 Exposure

The following parameters will be calculated for all study drugs:

- Duration of regimen: Minimum(Cutoff date, max(last dose date + 20 days if q3w/13 days if q2w/41 days if q6w for each study treatment, including NKTR-214, nivolumab, ipilimumab), date of death, date of end of study) - C1D1 + 1
- Duration of follow-up: Maximum (Min(date of last visit including survival follow-up, date of death) - C1D1 + 1, Duration of regimen)
- Duration of exposure to each study treatment (days): date of last dose - date of first dose + 1

- Number of cycles or doses for each study treatment (infusions): total number of cycles or doses (infusions) for which patient received treatment at planned or reduced (non-zero) level across all cycles.
- Calculated cumulative dose level for treatment administrated: 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.

See Table 3 for calculation of actual dose intensity, expected dose intensity, and relative dose intensity.

Table 3: Calculation of Actual Dose Intensity and Relative Dose Intensity for Each Study Medication

Study Drug and Dosing Regimen	Actual Dose intensity (mg/kg/week)[a]	Expected Dose Intensity (mg/kg/week)	Relative Dose Intensity (%)
NKTR-214 - 0.003 mg/kg Q2W (Part 1 only)	[Cumulative dose (mg/kg)[b] / (Exposure duration in days + 13 Days)] x 7	(0.003 mg/kg) / (2 weeks) = 0.0015 mg/kg/week	(Actual Dose intensity / Expected dose intensity) × 100
- 0.006 mg/kg Q3W	[Cumulative dose (mg/kg)[b] / (Exposure duration in days + 20 Days)] x 7	(0.006 mg/kg) / (3 weeks) = 0.002 mg/kg/week	
- 0.006 mg/kg Q2W (Part 1 only)	[Cumulative dose (mg/kg)[b] / (Exposure duration in days + 13 Days)] x 7	(0.006 mg/kg) / (2 weeks) = 0.003 mg/kg/week	
- 0.009 mg/kg Q3W (Part 1 only)	[Cumulative dose (mg/kg)[b] / (Exposure duration in days + 20 Days)] x 7	(0.009 mg/kg) / (3 weeks) = 0.003 mg/kg/week	
Nivolumab - 240 mg flat dose Q2W (Part 1 only)	{[(Total cumulative dose (mg)[c] / weight (kg) across all cycles)] / (Exposure duration in days + 13 Days)] }x 7	[(240 mg / weight (kg) across all cycles)] / (2 weeks)	Actual Dose intensity / Expected dose intensity) × 100
- 360 mg flat dose Q3W	{[(Total cumulative dose (mg)[c] / weight (kg) across all cycles)] / (Exposure duration in days + 20 Days)] }x 7	[(360 mg / weight (kg) across all cycles)] / (3 weeks)	
- 1 mg/kg Q3W	[Cumulative dose (mg/kg)[b] / (Exposure duration in days + 20 Days)] x 7	(1 mg/kg) / (3 weeks)= 0.3333 mg/kg/week	
- 3 mg/kg Q3W	[Cumulative dose (mg/kg)[b] / (Exposure duration in days + 20 Days)] x 7	(3 mg/kg) / (3 weeks) = 1 mg/kg/week	
Ipilimumab (Part 3 and Part 4 only) - 1 mg/kg Q6W	[Cumulative dose (mg/kg)[b] / (Exposure duration in days + 41 Days)] x 7	(1 mg/kg) / (6 weeks) = 0.16667 mg/kg/week	Actual Dose intensity / Expected dose intensity) × 100

Study Drug and Dosing Regimen	Actual Dose intensity (mg/kg/week)[a]	Expected Dose Intensity (mg/kg/week)	Relative Dose Intensity (%)
- 1 mg/kg Q3W	[Cumulative dose (mg/kg)[b] / (Exposure duration in days + 20 Days)] x 7	(1 mg/kg) / (3 weeks) = 0.3333 mg/kg/week	
- 3 mg/kg Q3W	[Cumulative dose (mg/kg)[b] / (Exposure duration in days + 20 Days)] x 7	(3 mg/kg) / (3 weeks) = 1 mg/kg/week	

a. For patients with dosing frequency switched, the calculation of Actual Dose Intensity will be depended on the dosing frequency of the last dose, e.g.,
   - If the last dose regimen is Q2W then Actual Dose Intensity = [Cumulative dose (mg/kg)[a] / (Exposure duration in days + 13 Days)] x 7
   - If the last dose regimen is Q3W then Actual Dose Intensity = [Cumulative dose (mg/kg)a / (Exposure duration in days +20 Days)] x 7

b. Cumulative dose (mg/kg) = Sum of "Total dose (mg) field from eCRF" across all treatment cycles / weight (kg) across all treatment cycles

c. For nivolumab 360 mg flat dose Q3W: Total cumulative dose (mg) = Sum of "Total dose (mg) field from eCRF" across all treatment cycles

7.0 STATISTICAL ANALYSES

7.1 Subject Disposition

Patient disposition summary will include the number and percentage of patients who were enrolled and who comprised each analysis population (safety, pharmacokinetic, DLT [Part 1 and Part 3 only], biomarker, immunogenicity, and response evaluable) by cohort (see Appendix 2 for details). The number and percentage of patients who discontinue from treatment (EOT) (NKTR-214, nivolumab, ipilimumab, and other anti-cancer therapy), discontinue from study (end of study [EOS]), both overall and by reason for EOT and EOS will be summarized.

All disposition data will be provided in a listing. In addition, patients who did not meet all inclusion and exclusion criteria will be listed separately.

7.2 Protocol Deviations

All protocol deviations are reported in Electronic Data Capture system and the management of protocol deviations are detailed in Protocol Deviation Management Plan.

The following deviations will be considered as important protocol deviations (IPD) and will be summarized.

- Patient not meeting certain key inclusion/exclusion criteria at study entry.
    - Patient received prior interleukin-2 (IL-2) therapy.
    - Patient does not have measurable disease per RECIST 1.1.
    - Patient has active brain metastases.

  - Patient does not meet inclusion/exclusion criteria for lab values (e.g., LDH, WBC, ANC, platelet count, hemoglobin, serum creatinine, ALT, AST, etc).
  - Patient does not have ECOG status as 0 or 1.
  - Patient needing more than 2 anti-hypertensive medications for managing hypertension.
  - Patient received prior palliative radiotherapy within 14 days before administration of first dose of study drug.

- Relative dose intensity >125% for NKTR-214 or nivolumab or ipilimumab (programmatically derived). Only when the overdose is affiliated with adverse events will be considered as IPD. The Part 1 patients who switched to RP2D when RP2D was determined are not considered as IPD. The Part 3 and 4 patients who switched to RP2D doublets when Part 3 and 4 were terminated are not considered as IPD.
- Patient receiving any antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, or investigational agent) while on study treatment..
- Critical consent issues: Patient didn't sign the informed consent for the study before first dose of the treatment (programmatically derived).

Prior to database lock, any other important deviations identified by Clinical will be reviewed and summarized together with the IPDs above.

7.3 Demographic and Baseline Characteristics

The following baseline characteristics will be summarized by cohort. All baseline presentations will identify participants with missing measurements.

- Age (descriptive statistics)
- Age category I (< 65, ≥ 65)
- Age category II (< 65, ≥ 65 and < 75, ≥ 75)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Other)
- Region (US/Canada, EU, Rest of World)
- ECOG Performance Status (0, 1) (for adults 18 years or older)
- M Stage at Study Entry - AJCC8 (M0, M1a, M1b, M1c, M1d) (source: CRF)
- M Stage at Study Entry – AJCC7 (M0,M1a,M1b,M1c) (Source: Medical adjudication)
- Stage at Most Recent Recurrence (III, IV)
- Stage at Initial Diagnosis (I/II/III/IV)
- Disease Classification at Study Entry
- Weight (descriptive statistics)

- Baseline PD-L1+ status based on a 1% cut off (≥ 1% vs. < 1% or indeterminate when collected)
- Baseline PD-L1+ status based on a 5% cut off (≥ 5% vs. < 5% or indeterminate when collected)
- Baseline PD-L1+ status based on a 10% cut off (≥ 10% vs. < 10% or indeterminate when collected)
- BRAF mutation status (BRAF mutant, wildtype) where applicable
- NRAS mutation status (NRAS mutant, wildtype)
- Baseline LDH (≤ ULN, > ULN)
- Baseline LDH (≤ 2*ULN, > 2*ULN)
- Baseline LDH (≤ 3*ULN, > 3*ULN)
- History of Brain Metastases (Yes, No)
- Time from Initial Disease Diagnosis to C1D1 (< 1 year, 1-< 2 years, 2-< 3 years, 3-< 4 years, 4-< 5 years, ≥ 5 years)
- All lesions (BICR Assessments at Baseline): sites of disease, number of disease sites per participant.
- Target lesions (Investigator and BICR Assessments at Baseline): Presence of target lesions, sum of reference diameters of target lesion.
- TMB (< median Mut/Mb vs >= median Mut/Mb)
- CD8 (< median score vs >= median score)
- IFNG Score (< median score vs >= median score).
- Reproductive Status (female only)
- Smoking History (current, former, never)

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

7.4 Cancer History

The summary of cancer history for the safety population will include stage at initial diagnosis, time from initial diagnosis to C1D1, stage at most recent recurrence, time from initial metastatic or locally advanced diagnosis to C1D1, history of brain metastases, and PD-L1 results. Additionally, disease specific history will be summarized for each tumor type.

All cancer history data will be provided in a listing.

7.5 Prior Anti-Cancer Therapy

The number and percentage of patients who received a prior neoadjuvant, adjuvant, locally advanced, or metastatic regimen will be summarized by cohort and histology.

All prior systemic therapies will be summarized by the World Health Organization Drug Dictionary Enhanced (WHODDE) using the Anatomical Therapeutic Chemical (ATC) Classification System level 2 term (therapeutic main group) and preferred term (PT). Patients will be counted only once within each ATC level 2 term and PT.

All prior cancer therapies will be provided in a listing.

7.6 Medical History and Prior Cancer Related Surgery

All medical history and surgery procedures prior to study enrollment will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 and summarized by system organ class (SOC) and preferred term (PT).

All medical history and prior cancer related surgery will be provided in a listing.

7.7 Prior, Concomitant and Follow-up Radiotherapy

Number and percentage of patients who have had prior, concomitant, or follow-up radiotherapy will be summarized by type of radiotherapy. Prior radiotherapy are radiotherapies with stop date prior to C1D1. Follow-up radiotherapies are defined as therapies with start date after the decision is made for the patient to discontinue from all study treatments. Otherwise, radiotherapies are considered as concomitant. For radiotherapy with incomplete start/stop date, comparison will be based on data available. If comparison is not feasible because of missing data, radiotherapy will be considered as prior, concomitant, and follow-up at the same time.

All radiotherapy will be provided in a listing.

7.8 Prior and Concomitant Medications and Procedures

All medications will be coded by the WHODrug Extended March 2016 B2 Version using ATC level 2 term and PT. Medications with start date prior to C1D1 are defined as prior medications otherwise they are defined as concomitant. Concomitant medications are defined as medications taken on or after the date of first 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, but before the last study dose + 100 days or date of initiation of new antineoplastic regimen - 1 day, whichever is earlier. Medications with incomplete stop date will be imputed according to the rules defined in Section 5.5.1.

All procedures performed during the study will be coded by MedDRA version 19.0 using SOC and PT.

All prior and concomitant medications and procedures will be listed.

7.9 Immune Modulating Medication

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

The percentage of subjects who received immune modulating concomitant mediations for the following will be reported by medication class and generic term.

- Management of drug-related select adverse event (any grade, grade 3-5) by select AE category/subcategory (see section 7.13.3 for select AEs)
- Management of imAEs (any grade, grade 3-5) by imAE category (see section 7.13.4 for imAEs)

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

- Percentage of subjects who received IMM

- Total duration of IMM use (excluding overlaps)

7.10 Subsequent Cancer Therapy

The number and percentage of patients who have subsequent cancer therapy will be summarized by ATC level 2 term and PT. Patients will be counted only once under each ATC level 2 term and preferred term.

All subsequent cancer therapy will be listed.

7.11 Study Exposure and Follow-Up

Duration of regimen, duration of follow-up, total number of cycles (based on NKTR-214), and duration of exposure for each study treatment will be summarized by descriptive statistics. For NKTR-214, nivolumab and ipilimumab, dose intensity, relative dose intensity, the number and percentage of patients who had cycles with dose delay dose reduction, dose infusion interruption, and corresponding reasons will be summarized.

All treatment exposure data will be listed by patient.

7.12 Efficacy Analysis

Given this is an open label non-comparative study, the efficacy analysis including ORR, CBR, and TTR will be summarized by descriptive statistics. The following parameters, DOR, PFS, and OS will be summarized by the Kaplan-Meier method.

Tumor response will be evaluated by Investigator per RECIST 1.1 and by BICR per RECIST 1.1, and irRECIST. Patients who achieve CR or PR will require confirmation (after 4 weeks). For patients who have subsequent cancer therapies, surgery or radiotherapy on target lesions, all data after the date of first subsequent cancer therapy or procedure will be excluded in any efficacy analysis.

All efficacy endpoints will be summarized by cohort (see Appendix 2 for details) and PD-L1 status. Selected efficacy endpoints maybe summarized for group of patients who have homogenous baseline, disease characteristics, or biomarker of interest identified during study.

The exact confidence interval for proportions will be based on the Clopper-Pearson method. The confidence interval for the quartiles of time to event variables will be based on the Brookmeyer and Crowley method.

All efficacy endpoints will be listed.

7.12.1 Best Overall Response, Objective Response Rate, and Clinical Benefit Rate

The primary endpoint for the efficacy analysis is the ORR per RECIST 1.1 at the RP2D for the doublet combination from Part 1 and 2 and at the RP2D for the triplet combination from Part 3 and 4.

All lesions including lymph nodes will be categorized as target or non-target lesions at baseline per RECIST 1.1 (Eisenhauer, 2009; also see Appendix 1) and evaluated at each post-baseline tumor assessment to determine the overall response as one of the following: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not-evaluable (NE). The BOR is

determined based on the overall response from each post-baseline tumor assessment in the following order: CR, PR, SD, PD, and NE. For CR and PR, tumor response must be confirmed by a subsequent assessment at least 4 weeks after the first CR or PR. For the confirmation of CR or PR, there could be multiple tumor assessments with overall response NE between the first and the subsequent CR or PR. Additionally for the confirmation of PR, there could be one SD between the first PR to the subsequent PR. For best response of SD, changes in tumor measurements must last for at least 7 weeks or longer from C1D1. Tumor assessment after the first PD, new systemic anti-cancer therapy, surgical procedures or radiotherapy on target lesions will not contribute to the BOR assessment.

The ORR is defined as the proportion of patients who have CR or PR as their BOR. The CBR is defined as the proportion of patients who have CR, PR, or SD (at least 7 weeks or longer from C1D1) as their BOR.

The primary analysis of ORR will be evaluated by Investigator per RECIST 1.1 and by BICR per RECIST 1.1, using the response evaluable population. Additional analyses of ORR will include tumor assessment based on Investigator and BICR per RECIST 1.1 using safety population. ORR by BICR is based on the BOR assessments by BICR.

Maximum percent change from baseline in the tumor size of target lesion per RECIST 1.1 by Investigator assessment and BICR will be summarized by waterfall plot. Tumor burden (tumor size based on the sum of reference diameters (longest for non-nodal lesions, short axis for nodal lesions) of all target lesions) overtime per RECIST 1.1 by Investigator and BICR will be summarized by spider plot. All waterfall and spider plots will be presented by PD-L1 categories of: negative (< 1%), positive (≥ 1%), and unknown.

Swimmer plots will be provided for patients' disposition status and tumor assessment results over time.

[redacted]

7.12.2 Time to Response

For patients who achieved CR or PR, the TTR is calculated as the time from the date of first dose to the date of first response (i.e. CR or PR). TTR will be summarized using descriptive statistics by Investigator assessment and BICR based on RECIST 1.1 using response evaluable population.

7.12.3 Duration of Response

For patients who achieved CR or PR, the DOR is calculated as the time between the first response (i.e., CR or PR) to progressive disease or death, whichever is earlier. DOR are subject to censoring rules specified for PFS in Section 7.12.4. DOR will be summarized by Investigator assessment and BICR based on RECIST 1.1 using the response evaluable population. The number and percentage of patients who have events or censored (including reasons for censoring), the quartiles (25%, median, and 75%) and 95% confidence interval by the Kaplan-Meier method will be provided.

7.12.4 Progression Free Survival

PFS is defined as the time between the date of first dose to the date of radiographic progressive disease per RECIST 1.1 or death due to any cause, whichever is earlier. For patients without PD or death, PFS will be censored following the rules specified below. PFS will be summarized following RECIST 1.1 for the safety population based on Investigator assessment and BICR using the Kaplan-Meier method. The summary will include number and percentage of patients who have event or censored (including reasons for censoring), quartiles (25%, median and 95% confidence interval, and 75%), and progression free rate every 6 months until 24 months.

The primary and secondary censoring rules for PFS are provided in Table 4.

Table 4: Censoring Rules for Progression Free Survival

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

7.12.5 Overall Survival

The overall survival (OS) is defined as the time between the date of first dose to the date of death from any cause. Patients who do not have date of death will be censored on the last date shown to be alive. OS will be summarized for the safety population using the Kaplan-Meier method. The summary will include number and percentage of patients who have an event or are censored (including reasons for censoring), quartiles (25%, median and 95% confidence interval, and 75%), and survival rate every 6 months up to 24 months.

7.12.6 Current Status of PFS and OS Follow-Up

The extent of follow-up defined as the time between C1D1 and last known date alive (for participants who are alive) or death date (for participants who died) will be summarized descriptively (median, min, max) in months for safety population.

7.12.7 Subgroup Analysis

Selected efficacy endpoints may be summarized separately for group of patients who have homogenous baseline, disease characteristics, or biomarker of interest identified during study. The following subgroups will be considered for all cohorts:

- Age (< 65 vs. ≥ 65; < 75 vs. ≥ 75)
- Gender (male vs. female)
- Race (white, black, Asian, other)
- Time from initial cancer diagnosis to first dose date (<1 year vs. ≥ 1 year)
- Patients with history of liver metastases; visceral metastases (Yes vs. No)
- Geographic region (US/Canada, EU, Rest of World)
- ECOG Performance status (0, 1, >1)
- Patients with history of brain metastases (Yes vs. No)
- PD-L1 status at baseline (>= 1% vs <1%) based on 28-8 TPS test results
- TMB (<median Mut/Mb vs >=median Mut/Mb)
- CD8 (< median score vs >= median score)
- IFNG Score (< median score vs >= median score).

Additionally, the following disease-specific subgroup will be considered:

For 1L Melanoma:

- M stage by American Joint Committee on Cancer (AJCC) version 8 (M1a, M1b, M1c, M1d)
- M stage by AJCC version 7 (M1a, M1b, M1c)
- Baseline LDH level (normal, high)
- Baseline BRAF status (mutant type, wild type)
- Baseline liver metastasis status (with or without liver metastasis)

For 1L RCC:

- International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score (favorable, intermediate, poor)

For 1/2L TNBC:

- Baseline PD-L1 by SP142 (IC <1%, IC ≥1%)

For 1L mUC:

- Baseline PD-L1 combined proportional score (CPS) (CPS Score < 1, CPS Score ≥ 1, CPS Score < 10, CPS Score ≥ 10)

If the number of patients in a subgroup has less than 10 per cohort, selected efficacy analysis will not be computed/displayed.

7.13 Safety Analyses

All safety analyses will be based on the overall safety population. Safety data will be summarized by the treatment received from study (See Section 3.3 for details): dose levels in Part 1 will be combined as one cohort (with the exception of DLT summary), RP2D in Part 1 and Part 2, NKTR-214 and nivolumab in combination with other anti-cancer therapies in Part 2, NKTR-214 in combination with nivolumab and ipilimumab in Part 3 and Part 4 unless otherwise specified (exceptions include CVA analysis in Section 7.13.5). Additionally, safety data will also be analyzed by tumor indications for patients who received RP2D.

7.13.1 Dose Limiting Toxicities

In Part 1 and Part 3, DLTs will be evaluated within the DLT evaluation window as specified in the protocol. Delayed DLTs are AEs that are defined in the protocol that occur after the DLT evaluation window. DLTs and delayed DLTs will be summarized separately by SOC and PT. All DLTs and delayed DLTs will be listed by patient.

7.13.2 Adverse Events

A treatment emergent adverse event (TEAE) is:

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

Incomplete start and end date for TEAEs will be imputed. Any AE will be considered as a TEAE if its status cannot be fully determined because of incomplete data. The treatment-emergent period will be defined as the period of time on or after the date/time of the first dose of study drug administration (on or after the date of the first dose of study drug administration, if time is not available) until the earlier date of the two dates:

- Date of initiation of new antineoplastic regimen – 1 day
- 30 days after the date of the last dose of all study drug.

All AEs will be coded by MedDRA version 19.0. The severity of AE will be determined based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade (version 4.03). A TEAE is considered as related to treatment if it is related to either NKTR-214 or

nivolumab or other anti-cancer therapy (a causality of 'related' or 'possibly related' is considered related to treatment). A TEAE is considered as leading to treatment discontinuation if it is leading to discontinuation of either NKTR-214 or nivolumab or other anti-cancer therapy. A TEAE is considered as leading to treatment delay, reduction or interruption if reported as leading to either NKTR-214 or nivolumab or anti-cancer dose delay, reduction or interruption. A TEAE is considered as leading to death if the severity grade is 5 or the outcome is fatal. A patient reporting the same TEAE multiple times will be counted only once within each SOC and PT under the highest severity and closest relationship.

Adverse events will be presented by summary tables and listings as outlined below:

The TEAE summary tables will include:

- Overall summary of TEAEs
- Overall summary of TEAE presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT
- Overall summary of any AEs that required immune modulating medication by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT
- Serious TEAE presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT
- TEAE presented by worst CTC grade (any grade, grade 3-4, grade 5) leading to any treatment dose delay, reduction, and interruption by SOC and PT
- TEAE presented by worst CTC grade (any grade, grade 3-4, grade 5) leading to discontinuation of any treatment by SOC and PT
- Related TEAE presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT

Additionally, TEAEs will be also be summarized in tables as follows:

- Grade 3 or above TEAE by PT
- Grade 3 or above related TEAE by PT
- Serious related TEAE by PT
- Related TEAE leading to discontinuation by PT
- Related TEAE leading to death by PT

For the following drug-related TEAE summary,

- Related TEAE presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT

treatment-emergent period based on time from the date of the first dose of study drug administration until the earlier date of the two dates will also be used:

- Date of initiation of new antineoplastic regimen – 1 day
- 100 days after the date of the last dose of all study drug

All AEs will be presented in listing as follows:

- SAEs,

- Grade 3 or above TEAEs,
- TEAE leading to any treatment dose delay, reduction, or interruption,
- TEAE leading to any treatment discontinuation,
- Fatal TEAEs

7.13.3 Adverse Events of Special Interest for Checkpoint Inhibitors

7.13.3.1 Select Adverse Events (to Support EU MAA)

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (e.g. pulmonary events, gastrointestinal events categories, etc.). Select AEs 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 (eg, 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 AEs. Multiple event terms that may describe each of these are grouped into endocrine, gastrointestinal (GI), hepatic, pulmonary, renal, and skin select AE categories, respectively.

Hypersensitivity/infusion reactions are analyzed along with the select AE 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 AEs.

The list of MedDRA 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 AEs, 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 AEs when applicable.

Further details on the definitions of select adverse event, time-to onset and time-to resolution are described in Appendix 3.

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

1) **Incidence of Select AE**

Select AEs will be summarized by treatment group for each category/subcategory.

- Overall summaries of any select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT.
- Overall summaries of any drug-related select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT.
- Overall summaries of any serious select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of drug-related serious select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of any select AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of drug-related select AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Summary of frequency of unique select AEs by Category or subcategory /PT (after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e. same PT) have been collapsed).

A by-subject select AE listing will be provided.

2) **Time-to Onset of Select AE**

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

Time-to onset analyses are restricted to treated participants who experienced at least one drug-related select AE in the category/subcategory.

3) **Time-to Resolution of Select AE**

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

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

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

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

7.13.3.2 Immune Mediated Adverse Events (imAEs) (to Support US BLA)

In order to further characterize AEs of special clinical interest, analysis of immune-mediated AEs (IMAE) will be conducted. The following imAEs will be grouped as potential non-endocrine or endocrine immune mediate adverse events:

- Non-endocrine imAEs include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash , and/or other specific events
- Endocrine imAEs include adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis

Non-endocrine imAEs must also meet the following criteria:

- Taking systemic steroid or immune-modulating medication on or after the onset of the AE and before the AE resolution date or
- The indication for a systemic steroid or immune-modulating medication is the AE
- Taking systemic corticosteroid or selected IMM or hormone replacement initiation was on or after the AE onset date and before the AE resolution date

All endocrine AEs will be considered as potential imAEs regardless if IMM and/or steroids are administered given these events may be treated with other medications outside of IMM and/or steroids.

All potential non-endocrine or endocrine imAEs along with concomitant medication information will be reviewed by Drug Safety, and Drug Safety will manually determine and provide a final list of non-endocrine or endocrine imAEs for the imAE summaries.

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

- Date of initiation of new antineoplastic regimen – 1 day
- 100 days after the date of the last dose of all study drug

ImAEs will be summarized by safety population and for each immune-mediated category:

- 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 by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT.
- Overall summary of endocrine imAEs leading to discontinuation 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) 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.
- Summaries of time-to onset and time-to resolution of non-endocrine imAEs presented by Category.

- Summaries of time-to onset and time-to resolution of endocrine imAEs presented by Category.

All imAEs including time to resolution will be listed.

Final selection and grouping of PTs and medications will be based on study team review prior to the final analysis.

7.13.3.3 Other Events of Special Interest

Other events of special interest (OEOSI) 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 same treatment-emergent period for imAE will be used for OEOSI.

The list of MedDRA preferred terms used to identify OEOSI 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.

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

7.13.4 Adverse Events of Special Interest to Bempegaldesleukin

7.13.4.1 Adverse Events of Special Interest

Adverse events of special interest for NKTR-214 consists of cerebrovascular accident (CVA) adverse events.

All analyses will be conducted for all patients in the safety analysis population, Part 1 and 2 RP2D doublet patients in the safety analysis population, and Part 3 and 4 patients in the safety analysis population.

Treatment-emergent period based on period of time from the date/time of the first dose of study drug administration until the earlier date of the following two dates will be used:

- Date of initiation of new antineoplastic regimen – 1 day
- 30 days after the date of the last dose of all study drug

Search list used to identify CVA events will be provided.

The following analyses will be conducted for Cerebrovascular accident (CVA) adverse events:

- Treatment-emergent adverse events of cerebrovascular accident (CVA) presented by PT (any grade, grade 5, serious).
- Subject incidence of cerebrovascular accident (CVA) by tumor type
- Medical history for subjects without and with treatment emergent adverse events of cerebrovascular accident (CVA)

7.13.4.2 Other AEs of Interest

Other AEs of interest (OAEOI) for NKTR-214 consists of the following:

- Hypotension (HoTN)
- IL-2 mediated AEs
  - Flu-like symptoms
  - Rash and pruritus
  - Fatigue/asthenia
  - Elevated hepatic transaminases
  - Elevated serum creatinine
- Infusion-related reaction (IRR, same day or next day post NKTR-214 administration)
- Eosinophilic disorder
- Thyroid dysfunction
- Arthralgia
- Syncope
- Cytokine release syndrome/cytokine storm (CRS)
- Capillary leak syndrome (CLS)
- Atrial fibrillation and ventricular tachycardia (AF/VT)
- Torsade de pointes/QT prolongation (TdP)
- Seizure

All analyses will be conducted for all patients in the safety analysis population, and Part 1 and 2 RP2D doublet patients in the safety analysis population.

Treatment-emergent period based on period of time from the date/time of the first dose of study drug administration until the earlier date of the following two dates will be used:

- Date of initiation of new antineoplastic regimen – 1 day
- 30 days after the date of the last dose of all study drug

Collapsing and clustering of records will be implemented when applicable. For time to resolution analysis, record with the longest duration after event collapsing and clustering will be used for each patient (Appendix 3).

Search list used to identify OAEOI will be provided.

Lab values within 30 days of last dose of all study drug received or date of initiation of new antineoplastic regimen – 1 day, whichever is earlier, will be included in the analysis.

For HoTN, Syncope, Flu-like symptoms, Rash and pruritus, Fatigue/asthenia, Arthralgia, CRS, CLS, the following analyses will be conducted:

- Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- NKTR-214 Related Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- Serious Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- Treatment-Emergent Adverse Events of OAEOI Leading to NKTR-214 Discontinuation by Worst CTC Grade presented by PT (any grade, grade 3-4).
- Time to the First Onset of Treatment Emergent Adverse Events of OAEOI (any grade)
- Time to Resolution of Treatment Emergent Adverse Events of OAEOI (any grade)
- Frequency of Treatment Emergent Adverse Events of OAEOI by Cycle by Worst CTC Grade (any grade, grade 3-5)

In addition, the following will be conducted for HoTN and Syncope:

- Medical history of subjects without and with Grade 3 and Above Treatment Emergent Adverse Events of OAEOI presented by SOC and PT

In addition, the following will be conducted for Arthralgia:

- Medical history of subjects without and with Treatment Emergent Adverse Events of OAEOI presented by SOC and PT

For AF/VT, TdP and seizure, the following analyses will be conducted:

- Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- NKTR-214 Related Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- Serious Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- Treatment-Emergent Adverse Events of OAEOI Leading to NKTR-214 Discontinuation by Worst CTC Grade presented by PT (any grade, grade 3-4).
- Time to the First Onset of Treatment Emergent Adverse Events of OAEOI (any grade)

For IRR, events that start after NKTR-214 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 NKTR-214 administration; otherwise, AEs that start on the same day as NKTR-214 administration will be included.

- Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- NKTR-214 Related Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- Serious Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- Treatment-Emergent Adverse Events of OAEOI Leading to NKTR-214 Discontinuation by Worst CTC Grade presented by PT (any grade, grade 3-4).
- Time to Resolution of Treatment Emergent Adverse Events of OAEOI
- Frequency of Treatment Emergent Adverse Events of OAEOI by Cycle by Worst CTC Grade
- Medical history of subjects without and with Grade 3 and Above Treatment Emergent Adverse Events of OAEOI presented by SOC and PT

For Elevated hepatic transaminases, Elevated serum creatinine and Eosinophilic disorder, the following analyses will be conducted based on AE data:

- Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- NKTR-214 Related Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- Serious Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).
- Treatment-Emergent Adverse Events of OAEOI Leading to NKTR-214 Discontinuation by Worst CTC Grade presented by PT (any grade, grade 3-4).

In addition, the following analysis will be conducted based on laboratory data:

- Frequency of Post-Baseline ALT/AST Laboratory Abnormal Elevations by Cycle and by Worst CTC Grade
- Figure of Central Tendency of Serum Creatinine Ratio (vs Baseline) by Baseline Grade
- Summary of Acute Kidney Injury KDIGO Staging based on Serum Creatinine Values
- Summary of Post-Baseline Eosinophil Elevations
- Treatment Emergent AEs for Subjects with Post-Baseline Eosinophil Elevations presented by SOC and PT (any grade, grade 3-5, serious)

For thyroid dysfunction, AE based analyses are referred to imAE relevant subcategories. In addition, the following analysis will be conducted:

- Summary of Hypothyroidism Identified by Laboratory Abnormalities or Thyroid Therapy Use
- Listing of Thyroid Therapy use for Subjects with Baseline Normal TSH/T4FR Lab Values and Prior Thyroid Therapy Use

Table 5: Summary of AE Based Analyses for Other AESI

Title	HoTN; Syncope	Arthralgia	Flu-like Symptom; Rash;	Fatigue; CRS; CLS;	AF/VT; TdP; Seizure	IRR[a]	Elevated Hepatic Transaminases; Elevated sCr; Eosinophilic disorder; [b]
Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).	Y	Y	Y	Y	Y	Y	Y
NKTR-214 Related Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).	Y	Y	Y	Y	Y	Y	Y
Serious Treatment-Emergent Adverse Events of OAEOI by Worst CTC Grade presented by PT (any grade, grade 3-4, grade 5).	Y	Y	Y	Y	Y	Y	Y
Treatment-Emergent Adverse Events of OAEOI Leading to NKTR-214 Discontinuation by Worst CTC Grade presented by PT (any grade, grade 3-4).	Y	Y	Y	Y	Y	Y	Y

Time to the First Onset of Treatment Emergent Adverse Events of OAEOI (any grade)	Y	Y	Y	Y	Y	N	N
Time to Resolution of Treatment Emergent Adverse Events of OAEOI (any grade) [c]	Y	Y	Y	Y	N	Y	N
Frequency of Treatment Emergent Adverse Events of OAEOI by Cycle by Worst CTC Grade (any grade, grade 3-5) [c]	Y	Y	Y	Y	N	Y	N
Medical history of subjects without and with (Grade 3 and Above) Treatment Emergent Adverse Events of OAEOI presented by SOC and PT[c] [d]	Y	Y	N	N	N	Y	N

[a] For IRR, events that start after NKTR-214 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 NKTR-214 administration; otherwise, AEs that start on the same day as NKTR-214 administration will be included.

[b] Additional analyses based on laboratory data will be conducted for Elevated hepatic transaminases, Elevated serum creatinine, Eosinophilic disorder, and thyroid disfunction. AE based thyroid disfunction analyses refer to imAE analysis subcategories.

[c]Collapsing and clustering of records will be implemented when applicable. For time to resolution analysis, record with longest duration after event collapsing and clustering will be used (APPENDIX 3).

[d] MH analysis with be summarized for patients by Grade 3 and Above AEs of HoTN, Syncope, and IRR (within defined window); MH analysis with be summarized by any grade AEs of arthralgia.

7.13.5 Deaths

Deaths will be summarized by treatment group:

- All deaths, reasons for death.
- Deaths within 30 days of last dose received or date of initiation of new antineoplastic regimen – 1 day, whichever is earlier, and reasons for death.
- Deaths within 100 days of last dose received or date of initiation of new antineoplastic regimen – 1 day, whichever is earlier, and reasons for death.

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

7.13.6 Clinical Laboratory Evaluation

7.13.6.1 Hematology

Hematology analytes include hemoglobin, platelet counts, and white (total leukocyte) blood cell counts and differentials (neutrophils and lymphocytes). Lab values within 30 days of last dose of all study drug received or date of initiation of new antineoplastic regimen – 1 day, whichever is earlier, will be included in the analysis. Worst CTC grade and shift table of worst CTC grade compared to baseline CTC grade will be summarized.

7.13.6.2 Serum chemistry

Serum chemistry analytes include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lipase, amylase, albumin, creatinine, urate, and total bilirubin. Lab values within 30 days of last dose of all study drug received or date of initiation of new antineoplastic regimen – 1 day, whichever is earlier, will be included in the analysis. Worst CTC grade and shift table of worst CTC grade compared to baseline CTC grade will be summarized.

7.13.6.3 Electrolytes

The following will be summarized by treatment group as worst CTC grade and as shift table of worst CTC grade compared to baseline CTC grade per subject: sodium (high and low), potassium (high and low), calcium (high and low), and glucose. Lab values within 30 days of last dose of all study drug received or date of initiation of new antineoplastic regimen – 1 day, whichever is earlier, will be included in the analysis.

7.13.6.4 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 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 7 days) ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN
- Concurrent (within 7 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

The window for this analysis is defined as the period of time after the first dose of study drug administration until the earlier date of the two dates:

- Date of initiation of new antineoplastic regimen – 1 day
- 30 days after the date of the last dose of all study drug.

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

7.13.6.5 Pregnancy Tests

The number and percentage of patients with positive result based on serum or urine pregnancy tests will be provided. Listing of pregnancy tests will be provided.

7.13.7 Vital Signs

Vital signs include height, weight, heart rate, respiratory rate, temperature, supine systolic blood pressure, supine diastolic blood pressure and oxygen saturation. Descriptive statistics will be provided for each vital sign at baseline, and maximum change from baseline during the study.

All vital sign data will be listed by patient.

7.13.8 Electrocardiogram

Electrocardiogram (ECG) assessment include PR, RR, QRS, QT, corrected QT interval using Fridericia's formula (QTcF), corrected QT interval using Bazett's formula (QTcB), and heart rate.

The number and percentage of patients in each of the following categories based on PR, QRS and HR will be provided for all Part 1 patients and all RP2D doublet patients in the safety population:

- PR outliers (PR > 200 msec and a 25% or greater increase from baseline)
- QRS outliers (QRS > 100 msec and a 25% or greater increase from baseline)
- HR outliers (HR < 50 beats/min and a 25% or greater decrease from baseline)
- HR outliers (HR > 100 beats/min and a 25% or greater increase from baseline)

The number and percentage of patients in each of the following categories based on QTcB and QTcF will be provided for all Part 1 patients and all RP2D doublet patients in the safety population:

- QTc interval ≤ 450 vs > 450 ms,
- QTc interval ≤ 450 vs > 480 ms,
- QTc interval ≤ 450 vs > 500 ms,
- QTc interval change from baseline ≤ 30 ms,> 30 ms and <= 60 ms, > 60 ms.

All ECG and echocardiogram data will be listed. A QTc exposure response analysis was conducted under a separate analysis plan and was summarized in a separate report which will be included in the CSR.

8.0 IMMUNOGENICITY

8.1 General Analysis Considerations

Validated methods to detect anti-PEG, anti-NKTR-214, anti-IL-2, anti-nivolumab, and anti-ipilimumab anti-drug antibodies (ADA) will be used to analyze immunogenicity samples. Immunogenicity sample testing will be done in tiers. Samples will be first tested with screening electrochemiluminescence assays (ECLA). Putative positive samples for anti-nivolumab, anti-ipilimumab, anti-NKTR-214 or anti-IL-2 ADAs will then be analyzed in a competition ECLA to confirm positivity. Confirmed anti--NKTR-214 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 NKTR-214. Confirmed positive samples from each assay (anti-nivolumab, anti-ipilimumab, anti-NKTR-214 and anti-IL-2) will then be tested to obtain a titer. Samples confirmed to be positive for anti-NKTR-214, anti-IL-2 and anti-nivolumab ADA will also be tested for neutralizing activity for IL-2 and nivolumab using validated cell-based assays.

8.2 Immunogenicity Measurements and Endpoints

The immunogenicity analysis will be performed separately for NKTR-214, nivolumab and ipilimumab. The data will be summarized for anti-NKTR-214, anti-PEG, anti-IL-2, anti-nivolumab and anti-ipilimumab antibodies and will be reported by sample and patient status.

For sample status, immunogenicity data will be summarized by the number and percentage of confirmed anti-drug antibodies to NKTR-214, PEG, IL-2, nivolumab and ipilimumab by analyte and visit. The samples will be classified as baseline ADA-positive, if ADA is detected 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 (positive seroconversion) in a sample from a patient who was baseline negative, or if there is at least 4-fold or greater ($\geq$) increase in ADA titer in comparison to the baseline positive titer.

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-IL2, anti-nivolumab and anti-ipilimumab 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 ($\geq$) than baseline positive titer (also known as 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 1 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 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 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. Subjects 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.

8.3 Safety Evaluation of ADA

All patients with ADA as mentioned above will be assessed for infusion related reactions (including hypersensitivity/angioedema/anaphylaxis) and will be compared against ADA negative patients.

8.4 Definitions

There are two sets of definitions: one for categorizing individual samples (**Error! Reference source not found.**) and another for categorizing patient responses (Table 7: ADA Response Categories: Patient Level

).

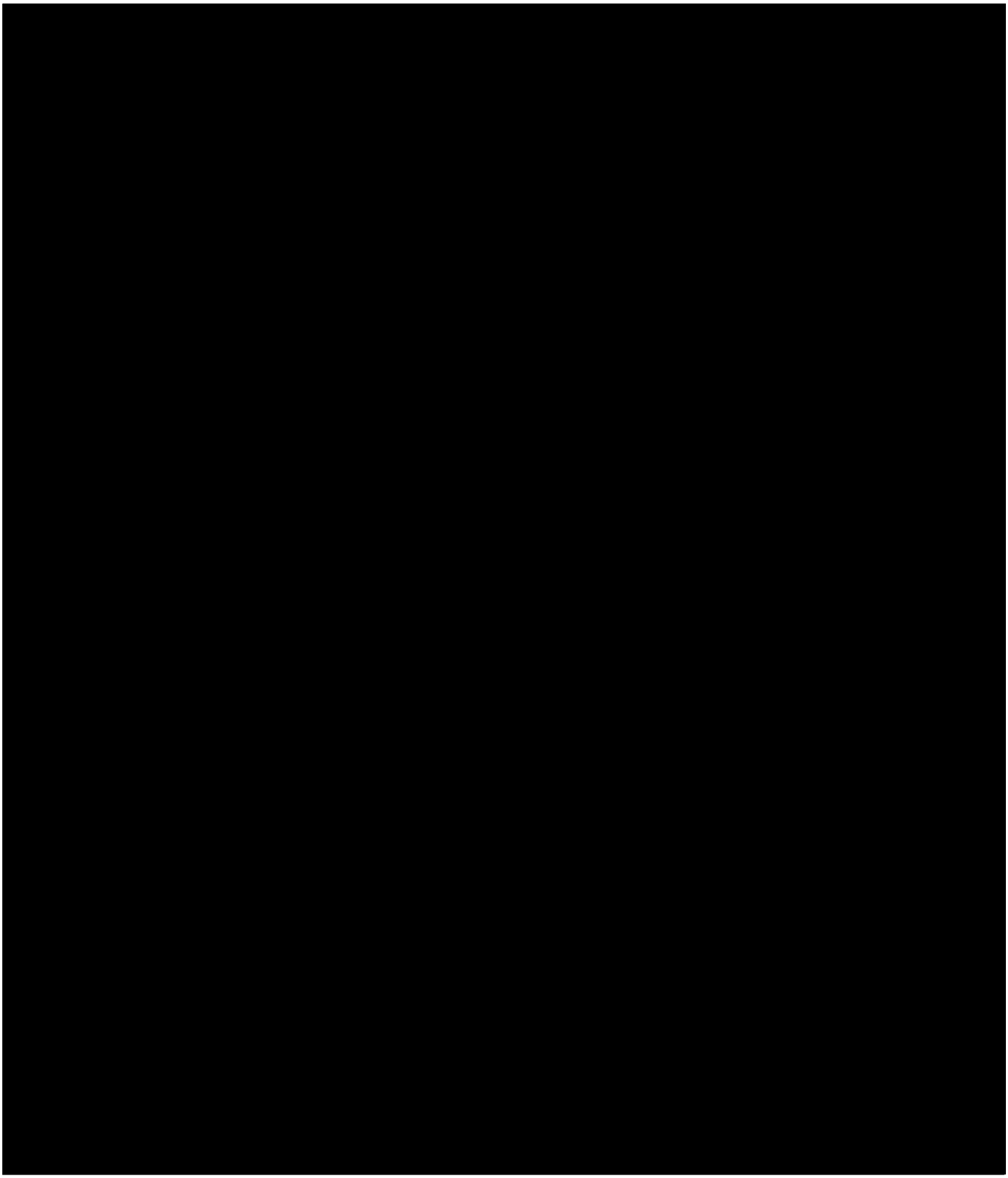
Table 6: ADA Status: Individual Samples

ADA Status	Definition
Baseline Negative	ADA is not detected in the last sample before initiation of treatment

ADA Status	Definition
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
Anti-Ipilimumab ADA-positive sample	After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a patient for whom anti-Ipilimumab ADA is not detected at baseline, *or* (2) an ADA detected sample with anti-Ipilimumab titer to be at least 4-fold or greater (≥) than baseline positive titer
ADA-Negative	After initiation of treatment, assay result is not a positive sample relative to baseline, i.e., increase from baseline is <4-fold

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



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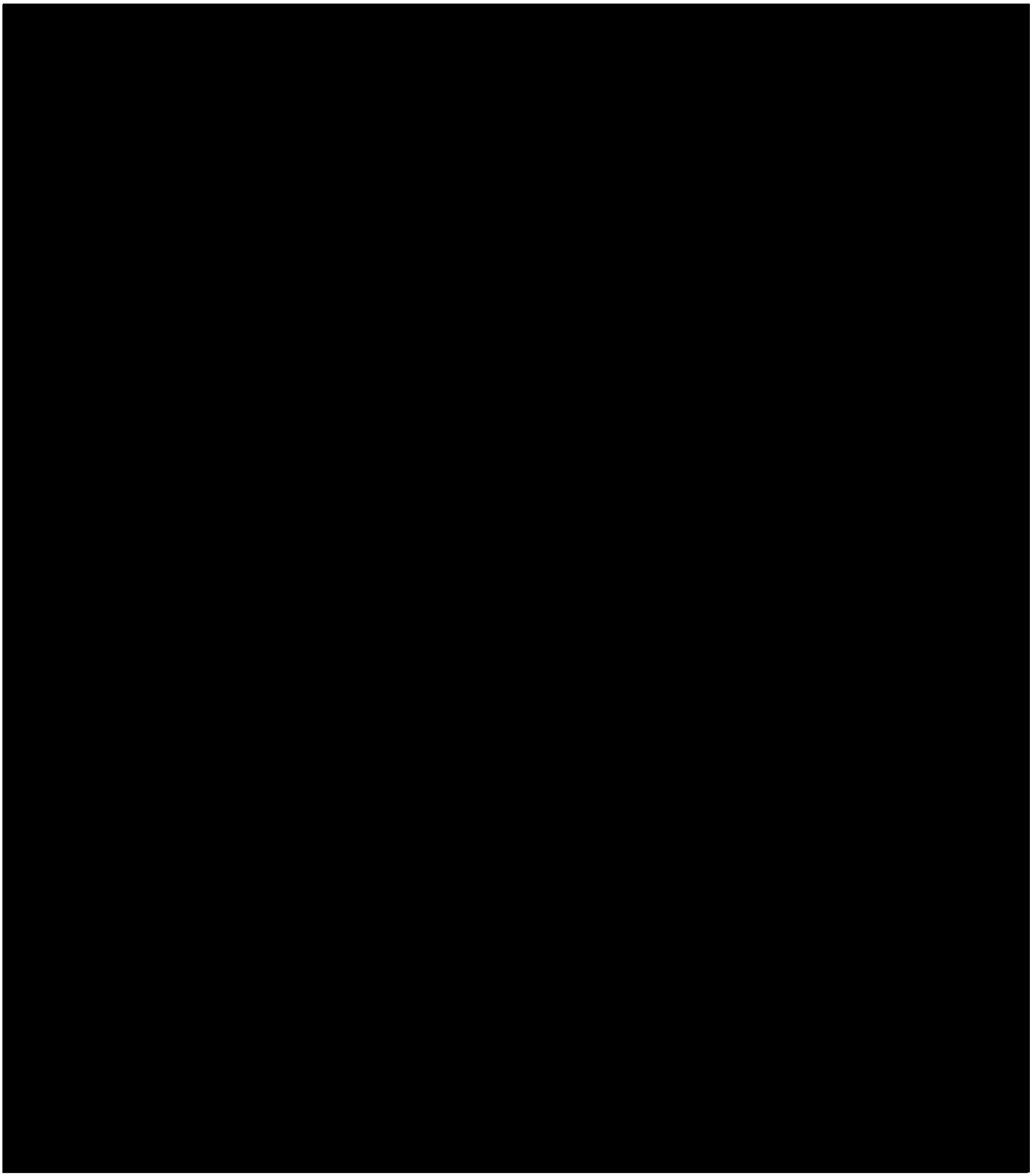

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10.0 PHARMACOKINETICS

10.1 Objectives of the Pharmacokinetic Analysis

In addition to the objectives described in this section, PK data obtained in this study may also be combined with data from other studies to develop population PK models. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of NKTR-214 related molecules 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, CL volume, half-life) and for NKTR-214 (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. Population PK analysis will be specified in a separate analysis plan and results of any population PK and/or exposure-response analyses will be reported separately.

10.1.1 Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) will consist of 5 different analyses. The PKAS includes all patients who received at least 1 dose of NKTR-214 and at least 1 measurable concentration of:

- NKTR-214-RC (related cytokine) PKAS: NKTR-214-RC
- NKTR-214-AC (active cytokine) PKAS: NKTR-214-AC
- Total-PEG PKAS: Total-PEG
- Nivolumab PKAS: Nivolumab
- Ipilimumab PKAS: Ipilimumab

10.2 General Analysis Considerations and Definitions

10.2.1 Pharmacokinetic Parameters

For Cycle 1 (all patients) and Cycle 2 (Part 1 only), PK parameters will be derived by Phoenix WinNonlin (version 8.3 or higher) based on noncompartmental (NCA) methods. PK parameters (Table 11) will include C_{max}, T_{max}, AUC_{last}, AUC_{inf} (for Cycle 1 only), V_z, CL, and $t_{1/2}$ for NKTR-214-RC, NKTR-214-AC, and Total-PEG. For NKTR-214-RC and NKTR-214-AC, $AUC_{0\text{-}96h}$, $AUC_{0\text{-}168h}$ may also be derived. Time zero will be defined as the start time of the infusion. Linear-up/log-down NCA methods will be used to estimate AUC. For Cycle 2 and beyond, the predose concentration may be duplicated as the last time point in the previous cycle for the calculation of PK parameters.

NCA PK parameters will only be derived when all requirements are met per Table 12. Where requirements are not met, PK parameter values will be reported as "not determinable".

Table 11: Pharmacokinetic Parameter Definitions

PK Parameter	Description
AUC_{inf}	Area under the concentration-time curve calculated from time 0 to infinity
AUC_{last}	Area under the concentration-time curve calculated from time 0 to the last measurable concentration
$AUC_{0\text{-}96h}$	Area under the concentration-time curve calculated from time 0 to 96 hours after dosing
$AUC_{0\text{-}168h}$	Area under the concentration-time curve calculated from time 0 to 168 hours after dosing
CL	Systemic clearance
C_{max}	Maximum observed concentration following drug administration
$t_{1/2}$	Half-life: the time required for the concentration to reach half of its original value
T_{max}	Time to reach maximum concentration
V_z	Volume of distribution during the terminal elimination phase following intravenous administration

Table 12: 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/F, 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}

10.3 Pharmacokinetic Measurements and Endpoints

10.3.1 Presentation of Individual and Mean Data

Graphical presentations of concentration data by sampling time, including individual and group mean values, will be provided. For all cycles, summary statistics of concentration data by scheduled sampling time will be provided. PK samples that were collected outside the protocol accepted time windows will be excluded from summary tables and summary figures. Descriptive statistics of all PK parameters will include geometric and arithmetic means, sample size (n), standard deviation, CV% and CV% geometric mean, median, minimum and maximum.

10.3.1.1 Handling of Missing Values, BLQ Values, and Outliers

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

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

When calculating PK parameters, all Cycle 1 pre-dose concentrations that are below the limit of quantification (BLQ) will be set to 0; all other concentrations that are BLQ will be set to missing.

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

- Nivolumab and ipilimumab

Missing pre-dose concentration values (except for pre-dose C1D1) will be imputed as LLOQ/2. Listings for pre-dose concentrations values (except for pre-dose C1D1) will list these concentrations as <LLOQ.

11.0 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

No changes from the protocol specified analyses are planned.

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13.0 APPENDICES

APPENDIX 1: EVALUATION OF OVERALL RESPONSE USING RECIST 1.1

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	PR[a]
CR	SD:	SD provided minimum criteria for SD duration met, otherwise, PD.
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD.
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE.
PR	CR	PR, except if next time point is CR, then overall CR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD.
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE.
NE	NE	NE

Abbreviations CR, complete response, PR, partial response, SD, stable disease, PD, progressive disease, and NE, not evaluable.

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

Source: Eisenhauer, 2009

APPENDIX 2: COHORT GROUPS IN THE FINAL ANALYSIS

Cancer Diagnosis in EDC [Cohort #, if applicable]	Name Used in Study Phase	Final Analysis and Reporting Cohort	Treatment
Melanoma	Part 1	1L MEL	NKTR 0.006 Q2W/NIVO 240 Q2W, NKTR 0.006 Q3W/NIVO 240 Q2W, NKTR 0.006 Q3W/NIVO 360 Q3W
MEL (1L) [1A]	Part 2	1L MEL RP2D	NKTR 0.006 Q3W/NIVO 360 Q3W
MEL 1L []	Part 3	Triplet 1L Melanoma Schedule 2	NKTR 0.006 Q3W/NIVO 1MG Q3W/IPIL 3 Q3W
MEL 1L ADJ [1D]	Part 2	MEL 1L ADJ	NKTR 0.006 Q3W/NIVO 360 Q3W
MEL 2-3L, I-O RELAPSE/ REFRACTORY [1B]	Part 2	MEL 2-3L Anti-PD(L)1	NKTR 0.006 Q3W/NIVO 360 Q3W
MEL 2L ANTI-PD(L)1 RR BRAFWT [1C]	Part 2	MEL 2L Anti-PD(L)1 BRAFWT	NKTR 0.006 Q3W/NIVO 360 Q3W
RENAL CELL CARCINOMA	Part 1	1L RCC	NKTR 0.003 Q2W/NIVO 240 Q2W, NKTR 0.006 Q2W/NIVO 240 Q2W, NKTR 0.006 Q3W/NIVO 360 Q3W, NKTR 0.009 Q3W/NIVO 360 Q3W
RENAL CELL CARCINOMA	Part 1	2L RCC I-O Naïve (If the patient received prior systemic therapy in locally advanced or metastatic setting)	NKTR 0.003 Q2W/NIVO 240 Q2W, NKTR 0.006 Q2W/NIVO 240 Q2W, NKTR 0.006 Q3W/NIVO 240 Q2W, NKTR 0.006 Q3W/NIVO 360 Q3W, NKTR 0.009 Q3W/NIVO 360 Q3W
RCC 1L [2A]	Part 2	1L RCC R2PD	NKTR 0.006 Q3W/NIVO 360 Q3W
RCC 2-3L ANTI-PD(L)1 RR [2B][a]	Part 2	RCC 2-3L ANTI-PD(L)1 RR	NKTR 0.006 Q3W/NIVO 360 Q3W
RCC (2-3L, I-O RELAPSE/ REFRACTORY) [2B][a]	Part 2	RCC 2-3L ANTI-PD(L)1 RR	NKTR 0.006 Q3W/NIVO 360 Q3W
RCC OTHER [2C]	Part 2	RCC - Other	NKTR 0.006 Q3W/NIVO 360 Q3W
RCC 1L []	Part 3	Triplet 1L RCC	NKTR 0.006 Q3W/NIVO 360 Q3W/IPIL 1 Q6W, NKTR 0.006 Q3W/NIVO 3MG Q3W/IPIL 1 Q3W
RCC 1L [10A.3]	Part 4	Triplet 1L RCC Schedule 3	NKTR 0.006 Q3W/NIVO 3MG Q3W/IPIL 1 Q3W
UROTHELIAL 1L [4A.2]	Part 2	UCC 1L REFUSED SOC	NKTR 0.006 Q3W/NIVO 360 Q3W

Cancer Diagnosis in EDC [Cohort #, if applicable]	Name Used in Study Phase	Final Analysis and Reporting Cohort	Treatment
UROTHELIAL 1L CIS-INELIGIBLE [4A.1]	Part 2	UCC 1L CIS-INEL	NKTR 0.006 Q3W/NIVO 360 Q3W
UROTHELIAL 3L, I-O RELAPSE/ REFRACTORY [4B][a]	Part 2	UCC 2-3L ANTI-PD(L)1 RR	NKTR 0.006 Q3W/NIVO 360 Q3W
UCC 2-3L ANTI-PD(L)1 RR [4B][a]	Part 2	UCC 2-3L ANTI-PD(L)1 RR	NKTR 0.006 Q3W/NIVO 360 Q3W
UROTHELIAL 3L, I-O RELAPSE/ REFRACTORY [4C]	Part 2	UCC - Other	NKTR 0.006 Q3W/NIVO 360 Q3W
UCC 1L []	Part 3	Triplet 1L UCC Schedule 2	NKTR 0.006 Q3W/NIVO 1MG Q3W/IPIL 3 Q3W
TNBC 1-2L I-O NAIVE [5A][b]	Part 2	TNBC 1-2L I-O NAÏVE (5a)	NKTR 0.006 Q3W/NIVO 360 Q3W
TNBC 1-2L, I-O THERAPY NAIVE [5A][b]	Part 2	TNBC 1-2L I-O NAÏVE (5a)	NKTR 0.006 Q3W/NIVO 360 Q3W
HR POS BC I-O NAIVE CHEMO [6B]	Part 2	HR POS BC I-O NAÏVE CHEMO	NKTR 0.006 Q3W/NIVO 360 Q3W
GC 2-3L I-O NAIVE [7]	Part 2	GC 2-3L I-O NAÏVE	NKTR 0.006 Q3W/NIVO 360 Q3W
CRC 2-3L I-O NAIVE MSI-HIGH [8A]	Part 2	CRC 2-3L I-O NAÏVE MSI-HIGH	NKTR 0.006 Q3W/NIVO 360 Q3W
CRC 3L I-O NAIVE MSI-NON HIGH [8B]	Part 2	CRC 3L I-O NAIVE MSI-NON HIGH	NKTR 0.006 Q3W/NIVO 360 Q3W
NON-SMALL CELL LUNG CANCER	Part 1	Depending on PD-L1 Central Test assigned to one of the following cohorts NSCLC 1L PD-L1 <1% NSCLC 1L PD-L1 ≥1%- <50% NSCLC 1L PD-L1 ≥50% NSCLC 1L PD-L1 Missing	NKTR 0.003 Q2W/NIVO 240 Q2W, NKTR 0.006 Q3W/NIVO 360 Q3W, NKTR 0.009 Q3W/NIVO 360 Q3W
NON-SMALL CELL LUNG CANCER	Part 1	NSCLC 2L I-O NAÏVE FOLLOWING PLAT (If the patient received prior systemic therapy in	NKTR 0.006 Q3W/NIVO 360 Q3W

Cancer Diagnosis in EDC [Cohort #, if applicable]	Name Used in Study Phase	Final Analysis and Reporting Cohort	Treatment
		locally advanced or metastatic setting)	
NSCLC 1L [11A.1]	Part 3	Triplet 1L NSCLC Schedule 1	NKTR 0.006 Q3W/NIVO 360 Q3W/IPIL 1 Q6W
NSCLC 1L [11A.1]	Part 4	Triplet 1L NSCLC Schedule 1	NKTR 0.006 Q3W/NIVO 360 Q3W/IPIL 1 Q6W
NSCLC 1L NONSQ PLAT/ PEM MAIN [3D.1]	Part 2	NSCLC 1L NONSQ PLAT/PEM MAIN	NKTR 0.006 Q3W/NIVO 360 Q3W+Chemo
NSCLC 1L PD-L1 < 1% [3A.1]	Part 2	Depending on PD-L1 Central Test assigned to one of the following cohorts NSCLC 1L PD-L1 <1% NSCLC 1L PD-L1 ≥1%- <50% NSCLC 1L PD-L1 ≥50% NSCLC 1L PD-L1 Missing	NKTR 0.006 Q3W/NIVO 360 Q3W
NSCLC 1L PD-L1 >= 1% - < 50% [3A.2]	Part 2	Depending on PD-L1 Central Test assigned to one of the following cohorts NSCLC 1L PD-L1 <1% NSCLC 1L PD-L1 ≥1%- <50% NSCLC 1L PD-L1 ≥50% NSCLC 1L PD-L1 Missing	NKTR 0.006 Q3W/NIVO 360 Q3W
NSCLC 1L PD-L1 >= 50% [3A.3]	Part 2	Depending on PD-L1 Central Test assigned to one of the following cohorts NSCLC 1L PD-L1 <1% NSCLC 1L PD-L1 ≥1%- <50% NSCLC 1L PD-L1 ≥50% NSCLC 1L PD-L1 Missing	NKTR 0.006 Q3W/NIVO 360 Q3W

Cancer Diagnosis in EDC [Cohort #, if applicable]	Name Used in Study Phase	Final Analysis and Reporting Cohort	Treatment
NSCLC, I-O RELAPSE/ REFRACTORY [3C][a]	Part 2	NSCLC 2-3L ANTI-PD(L)1 RR	NKTR 0.006 Q3W/NIVO 360 Q3W
NSCLC 2-3L ANTI-PD(L)1 RR [3C][a]	Part 2	NSCLC 2-3L ANTI-PD(L)1 RR	NKTR 0.006 Q3W/NIVO 360 Q3W
NSCLC 2L FOLLOWING PLAT DBLT/ ANTI-PD-1 [3H]	Part 2	NSCLC 2L FOLLOWING PLAT/DBLT/ANTI-PD-1	NKTR 0.006 Q3W/NIVO 360 Q3W
NSCLC 2L, I-O THERAPY NAIVE [3B]	Part 2	NSCLC 2L I-O NAÏVE FOLLOWING PLAT	NKTR 0.006 Q3W/NIVO 360 Q3W
NSCLC IL SQ PLAT/ TAX [3E]	Part 2	NSCLC 1L SQ PLAT/TAX	NKTR 0.006 Q3W/NIVO 360 Q3W+Chemo
NSCLC OTHER [3I]	Part 2	NSCLC - Other	NKTR 0.006 Q3W/NIVO 360 Q3W

a. Name for these cohorts (2b, 3c, 4b) is changed from 'I-O RELAPSE/ REFRACTORY' to 'ANTI-PD(L)1 RR' in Protocol Amendment 5 and onwards.
b. Name in EDC was updated from 'TNBC 1-2L I-O NAIVE [5A]' to 'TNBC 1-2L I-O THERAPY NAIVE [5A]' in the middle of the study.

APPENDIX 3: TIME-TO ONSET AND TIME-TO RESOLUTION DEFINITION AND CONVENTIONS FOR SELECT ADVERSE EVENTS, IMMUNE-MEDIATED ADVERSE EVENTS AND EVENTS OF 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 13: Derivation of Clustered AE 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 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. This measure is defined only for subjects 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 13: Derivation of Clustered AE

Type of clustered AE	Derivation
Any grade	Collapse any on-treatment AE from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AE from the same category
Grade 3-5	Collapse any on-treatment AE 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 AE is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AE 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 AE 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).

[redacted]

[redacted]