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Nektar Therapeutics

CLINICAL STUDY PROTOCOL

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

Protocol Number: 16-214-02

Protocol Amendment Date: 18 June 2018

Protocol Amendment No. 6.0

Supersedes: Amendment 5.1 dated 09 January 2018
Amendment 5.0 dated 05 December 2017 (US)
4.0 dated 22 June 2017 (Canada, Belgium, Ukraine, US)
3.2 dated 07 August 2017 (France)
3.1 dated 03 April 2017 (Italy, Poland, Spain)

US IND Number: 125471

EudraCT Number: 2016-003543-11

Sponsor: Nektar Therapeutics
455 Mission Bay Boulevard South
San Francisco, CA 94158 USA

Sponsor's Medical Contact and Study Medical Monitor: [redacted]

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INVESTIGATOR SIGNATURE PAGE

Nektar Therapeutics

TITLE:	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
PROTOCOL NUMBER:	16-214-02
PHASE OF STUDY:	Phase 1/2
PROTOCOL DATE:	18 June 2018
STUDY SPONSOR:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

PRINCIPAL INVESTIGATOR COMMITMENT:

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that I understand my responsibilities pursuant to the Code of Federal Regulations (21 CFR § 312) and ICH E6 Good Clinical Practice guidelines, as well as with any and all applicable federal, state and/or local laws and regulations, and agree to conduct the study in accordance with the protocol referenced herein.

_____

Principal Investigator Printed Name

_____ _____

Principal Investigator Signature **Date**

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[redacted]

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LIST OF STUDY CONTACTS

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[redacted]	[redacted]	[redacted]

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ABBREVIATIONS

Abbreviation or Term	Definition
1L	first line
2L	second line
3L	third line
5-FU	fluorouracil
ACTH	adrenocorticotropic hormone
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ALP	alkaline phosphatase
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the curve
BOR	best overall response
BUN	blood urea nitrogen
C1D1, C2D1, C3D1, etc.	Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, etc
C_{avgss}	steady-state average concentration
C_{maxss}	steady-state peak concentration
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
cis	cisplatin
CL	clearance
C_{max}	maximum concentration
CR	complete response
CRC	colorectal carcinoma
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated protein 4
D5W	dextrose 5% in water for injection
DCI	data collection instrument
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response

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Abbreviation or Term	Definition
ECG	electrocardiogram
ECHO	echocardiogram
eCOA	electronic clinical outcomes assessments
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FNR	false-negative rate
FOLFIRI	5-fluorouracil, leucovorin, and irinotecan
FOLFOX	fluorouracil, leucovorin, and oxaliplatin
FPR	false-positive rate
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
Hgb	hemoglobin
HIV	human immunodeficiency virus
hr	hour(s)
HR	hormone receptor
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
IL-2	interleukin-2
IL2Rα	IL-2 receptor alpha subunit
IL2Rβ	IL-2 receptor beta subunit
imAE	immune-mediated adverse event
IND	Investigational New Drug application
I-O	immuno-oncology
IRB	institutional review board
irRECIST	immune-related RECIST

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Abbreviation or Term	Definition
IV	intravenous
kg	kilogram
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MAD	maximally administered dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MEL	melanoma
min	minute(s)
mg	milligram
mL	milliliter
mm Hg	millimeters of mercury
mo	month
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multigated acquisition
NCI	National Cancer Institute
NKTR-214/nivolumab/ipilimumab	triplet containing NKTR-214 and nivolumab and ipilimumab
NE	inevaluable
NK	natural killer
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PEG	polyethylene glycol
PFS	progression-free survival

Tannir NM, *et al. J Immunother Cancer* 2022; 10:e004419. doi: 10.1136/jitc-2021-004419

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Abbreviation or Term	Definition
PK	pharmacokinetic
pMMR	mismatch repair proficient
PPK	population pharmacokinetics
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
q1h × 2	every hour for 2 hours
q1h × 3	every hour for 3 hours
q1h × 4	every hour for 4 hours
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
q6w	every 6 weeks
QTcF	Fridericia's corrected QT interval
RBC	red blood cells
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-2	recombinant human interleukin 2
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLD	sum of the longest diameters
SCLC	small-cell lung cancer
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination phase half-life
T3	triiodothyronine
T4	free thyroxine
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
TNBC	triple-negative breast cancer
TP	total protein
Treg	regulatory T cell
TSH	thyroid stimulating hormone

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Abbreviation or Term	Definition
TTR	time to response
ULN	upper limit of normal
US	United States of America
V_d	volume of distribution
VEGF	vascular endothelial growth factor
WBC	white blood cell
WCBP	women of childbearing potential

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1.0 STUDY SYNOPSIS

Name of Sponsor:	Nektar Therapeutics
Name of Finished Products:	NKTR-214 drug product Opdivo® [redacted]
Name of Active Ingredients:	NKTR-214 drug substance Nivolumab (anti-PD-1) [redacted]
Title of Study:	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
Duration of Treatment:	Patients will be treated until disease progression, death, unacceptable toxicity, symptomatic deterioration, achievement of maximal response, the Investigator's decision to discontinue treatment, patient decision to discontinue treatment or withdraw consent, lost to follow up, or Nektar Therapeutics decides to terminate the trial. Treatment may continue beyond progression if there is clinical benefit as determined by the Investigator.
Phase of Development:	Phase 1/2
Objectives:	The primary objectives are: • To evaluate the safety and tolerability, and define the maximum tolerated dose (MTD) and/or recommended 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 The secondary objective is: • 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) The exploratory objectives are:

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	• To evaluate the efficacy of NKTR-214 in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies by assessing immune-related RECIST (irRECIST) at the RP2D • To assess the immunological effects in blood and the tumor environment, and to measure disease-specific pharmacodynamics markers such as lactate dehydrogenase (LDH) (e.g., in melanoma), of NKTR-214 when administered in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies • To characterize the pharmacokinetics (PK) of nivolumab, ipilimumab, NKTR-214, and NKTR-214 metabolites when NKTR-214 is administered in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies • To assess the development of anti-drug antibodies against NKTR-214, nivolumab, and ipilimumab when NKTR-214 is administered in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies • To assess the association between efficacy measures and PD-L1 expression in tumors, tumor and blood-based mutational burden, and inflammation status when NKTR-214 is administered in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies
Study Population:	Adults aged 18 years and older with select locally advanced or metastatic solid tumor malignancies who have measurable disease. [redacted] renal cell carcinoma (RCC), [redacted] urothelial carcinoma, [redacted]
Number of Patients (planned):	Part 1 (dose escalation: NKTR-214 plus nivolumab): Approximately 50 patients will be enrolled. Part 2 (dose expansion: NKTR-214 plus nivolumab or NKTR-214 plus nivolumab with other anti-cancer therapies): Approximately 925 patients will be enrolled. [redacted]
Number of Study Sites:	Approximately 65 sites
Countries:	Part 1: US Part 2: US, Canada, and Europe; additional countries may be added [redacted]

Study Design:

Part 1: Dose Escalation (NKTR-214 plus nivolumab)

NKTR-214, in escalating doses, will be combined with nivolumab. The first NKTR-214 dose and schedule to be studied (i.e., 0.006 mg/kg once every 3 weeks [q3w]) was determined based on an ongoing monotherapy trial with NKTR-214. The dose escalation scheme is provided below.

Part 1: Dose Escalation Scheme

Cohort	NKTR-214	Nivolumab q2w	Nivolumab q3w
1	0.006 mg/kg q3w	240 mg	
2	0.006 mg/kg q3w		360 mg
3	0.006 mg/kg q2w	240 mg	
4	0.009 mg/kg q3w		360 mg

For dose escalation cohorts the Safety Review Committee will jointly decide the following:

- Dose escalation to the next cohort and/or dose schedule
- RP2D
- Dose levels of NKTR-214 for a given cohort may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested.
- Decision to evaluate NKTR-214 and nivolumab in additional patients at lower NKTR-214 doses and different dose schedules to assess the benefit/risk profile within the anticipated total number of patients.

DLT evaluation will be based on the study dose schedule as detailed in Section 5.11.

The Sponsor may choose to concurrently enroll patients and dose NKTR-214 at lower dose levels and/or different dose schedules to assess the benefit/risk profile within the anticipated 50 patients. The Sponsor may also evaluate other doses and dose schedules based on the safety findings from ongoing clinical trials.

Determination of the Recommended Phase 2 Dose:

As of October 05, 2017, the safety of NKTR-214 in combination with nivolumab has been established in 38 patients across 5 dose cohorts. In the highest dose tested, NKTR-214, 0.009 mg/kg + 360 mg nivolumab, two patients experienced a DLT. One patient had Grade 3 hypotension and a second patient experienced Grade 4 metabolic acidosis, each of which resolved within 5 days and the patients continued on treatment at a lower dose of NKTR-214. At the data cut of October 05, 2017, there were 34 patients with at least 1 post-treatment tumor scan, including 10 with metastatic melanoma, 19 with renal cell carcinoma (RCC), and 5 with non-small cell lung cancer (NSCLC). Of these 34 response-evaluable patients, 24 were treated at 0.006 mg/kg NKTR-214 with nivolumab 360 mg flat dose q3w; 17 patients had partial or complete responses and 13 had stable disease. There were no Grade 3 TRAEs in the 25 patients treated at this dose. The dose escalation portion for NKTR-214 and nivolumab (Part 1) is complete, with the RP2D established at 0.006 mg/kg NKTR-214 with nivolumab 360 mg flat dose q3w.

Part 2: Dose Expansion (NKTR-214 plus nivolumab ± other anti-cancer therapies)

Approximately 925 patients (18-39 patients per indication, except for Cohort 3h in which target enrollment may be approximately 100 patients, depending on early

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efficacy results in the initial 20 evaluable patients) will be enrolled in the following cohorts:

Part 2 Cohorts: All Patients Receive NKTR-214 plus Nivolumab[a]		
Indication	Cohort	Description
[redacted]	[redacted]	[redacted]
RCC	2a[b]	1L
[redacted]	[redacted]	[redacted]
Urothelial	4a[b]	1L, cisplatin ineligible
	4a[b,c]	1L, refused standard of care
[redacted]	[redacted]	[redacted]

[redacted] BC = hormone-receptor positive, HER2-negative breast cancer; I-O = immuno-oncology; MSI = microsatellite instability; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; RP2D = recommended Phase 2 dose; SCLC = small cell lung cancer; TNBC = triple-negative breast cancer

a. All patients receive the RP2D: NKTR-214 0.006 mg/kg q3w with nivolumab 360 mg q3w

b. Cohorts open for enrollment before Amendment 6.

c. For sites located in Italy only: patients may not be enrolled if they have 1L urothelial cancer with cisplatin-eligible disease.

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The sponsor will notify sites when individual cohorts are open for screening and when screening is closed. Certain cohorts may only open at select participating sites.

Part 3: Schedule Finding for Triplet (NKTR-214, nivolumab, and ipilimumab)

[redacted]

Table 1: Example of Concurrent and Staggered Schedule Scenarios for Triplet (Dosing Schedule 1)

[redacted]

Table 2: Part 3 Cohort A: Concurrent Dosing Schedules

[redacted]

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[redacted]

Part 4: Dose Expansion of Triplet (NKTR-214 plus nivolumab plus ipilimumab)

[redacted]

Table 3: Part 4 Indications and Dosing Schedules

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

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Key Eligibility Criteria:	For the purposes of patient eligibility determination, note the following definitions: • For the purposes of eligibility, "neoadjuvant therapy" is defined as systemic chemotherapy administered prior to definitive local surgery in a patient without distant metastases; "adjuvant therapy" is defined as systemic therapy administered following definitive local therapy (surgery or radiation) in a patient without distant metastases (with no evidence of disease). • A "line of therapy" is defined as any regimen – single-agent or combination therapy, cytotoxic therapy, immuno-oncology therapy separately or in combination – that is given for patients with advanced disease, and that is stopped for any reason, including progression of disease, toxicity, physician decision, or patient withdrawal of consent. **For Parts 1-4** • Provide written, informed consent to participate in the study and follow the study procedures • Male or female patients, age 18 years or older at the time of signing the informed consent form (ICF) • Life expectancy > 12 weeks • Patients must not have received prior interleukin-2 (IL-2) therapy. • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 • Measurable disease per RECIST 1.1 • Fresh biopsy or recently obtained biopsy within the past 6 months without intervening treatment, and archival tumor tissue available **For Parts 1 and 2 (NKTR-214 plus nivolumab ± other anti-cancer therapies)** **For Disease-Specific Tumor Types** [redacted]

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- [redacted]

Renal Cell Carcinoma (RCC)

- Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC stage IV) RCC.
- Histologically confirmed RCC with a clear-cell component.

Cohort 2a – RCC (1L)

- Have not received prior anti-cancer therapy for advanced or metastatic RCC.
- Prior to disease metastasis, patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens, including, but not limited to, checkpoint inhibitors such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) antibody, or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways, indoleamine 2,3-dioxygenase pathway inhibitors, cancer vaccines, adoptive cell therapies, or other cytokine therapies.

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Urothelial Carcinoma

- Histologically or cytologically documented locally advanced or transitional cell carcinoma of the urothelium including renal pelvis, ureters, urinary bladder, or urethra. Patients with mixed histologies are required to have a dominant transitional cell pattern.

Cohort 4a – Urothelial Carcinoma (1L)

- Enrollment of urothelial carcinoma 1L patients will target accrual of up to 20 patients who are cisplatin-ineligible and up to 20 patients, who, after consultation with the Investigator, choose to forego front-line chemotherapy.
- Treatment naive patients who refuse chemotherapy standard of care or treatment naive, cisplatin-ineligible patients who meet at least one of the following criteria:
  - Creatinine clearance (calculated or measured) < 60 mL/min. Cisplatin-ineligible patients must have a creatinine clearance < 60 mL/min and GFR ≥ 30 mL/min.
  - Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade ≥ 2 audiometric hearing loss
  - CTCAE v4.03 Grade ≥ 2 peripheral neuropathy
- No prior chemotherapy for inoperable locally advanced or metastatic urothelial carcinoma. Prior local intravesical chemotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment.
- For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval of more than 12 months between the last treatment administration and the date of recurrence is required to be considered treatment naive in the metastatic setting. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

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	Cohort 13a.2 – <u>Urothelial Carcinoma (1L)</u>
	• Histologically or cytologically documented locally advanced or transitional cell carcinoma of the urothelium including renal pelvis, ureters, urinary bladder, or urethra. Patients with mixed histologies are required to have a dominant transitional cell pattern.
	• Treatment naive patients who refuse chemotherapy standard of care or treatment naive, cisplatin-ineligible patients who meet at least one of the following criteria:
	  ○ **Creatinine clearance (calculated or measured) < 60 mL/min. Cisplatin-ineligible patients must have a creatinine clearance < 60 mL/min and GFR ≥ 30 mL/min.**
	  ○ **Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade ≥ 2 audiometric hearing loss**
	  ○ **CTCAE v4.03 Grade ≥ 2 peripheral neuropathy**
	• No prior chemotherapy for inoperable locally advanced or metastatic urothelial carcinoma. Prior local intravesical chemotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment.
	• For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval of more than 12 months between the last treatment administration and the date of recurrence is required to be considered treatment naive in the metastatic setting. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

Test Product, Dose and Mode of Administration:	NKTR-214 administered IV over 30 (± 5) minutes at a starting dose of 0.006 mg/kg q3w Nivolumab (anti-PD-1) administered IV over 30 (± 5) minutes at either a 360 mg flat dose q3w (Parts 2, 3, and 4), [redacted]

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	• [redacted]
Safety:	Assessment of safety will be determined by an ongoing review of the following: • incidence of adverse events (AEs), including serious AEs (SAEs) • clinical laboratory tests (blood and urine sampling) • vital signs • electrocardiograms (ECG) and echocardiograms (ECHO) • physical examination
Pharmacokinetics:	Blood samples for PK analyses will be collected from all patients. Serial PK samples will be collected at multiple scheduled sampling times. Plasma concentrations of NKTR-214 and its metabolites will be measured for each PK sample using validated method(s). Serum concentrations of nivolumab and ipilimumab will be measured using validated methods. Pharmacokinetic parameters such as maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the curve (AUC), clearance (CL), volume of distribution (V_d), and half-life ($t_{1/2}$) will be estimated from plasma or serum concentration-time data where possible.
Pharmacodynamics:	Systemic and tumor tissue-based pharmacodynamic effects of NKTR-214 in combination with nivolumab and in combination with nivolumab and other anti-cancer therapies will be examined. Blood samples for systemic pharmacodynamic analyses will be collected pre- and post-combination treatment from all patients enrolled to assess the effects of the combination treatment on markers of immune system activation, and immune cell populations. Fresh tumor tissue will be collected pre- and post-treatment for characterization of tumor infiltrating lymphocytes (TILs) and immune system-related genes and proteins. Archival tumor tissue samples will be collected for analysis of immune system-related genes and proteins.
Efficacy:	Tumor measurements will be performed every 8 weeks ± 7 days. The primary efficacy measurement will be ORR (defined as the number of patients with a best overall response of complete response or partial response divided by the number of patients in the population of interest) by RECIST 1.1. Other efficacy outcomes will include: • best overall response (BOR) • time to response (TTR) • duration of response (DOR) • clinical benefit rate (CBR) • overall survival (OS) • progression-free survival (PFS)

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Statistical Methods:	**Safety:** Safety assessments will include adverse events, clinical laboratory tests, vital signs, physical examinations, echocardiograms, and ECGs. The incidence of DLTs will be evaluated for each dose escalation or dose schedule finding cohort. All treatment-emergent adverse events (TEAEs) will be summarized by system organ class and preferred term for each cohort in Part 1 and Part 3 and for each tumor type in the dose expansion phase (Parts 2 and 4). All TEAEs will be summarized by incidence, severity, and relationship to study drug(s). All immune-mediated AEs (imAEs) will be summarized separately. Clinical laboratory tests and vital signs will be summarized descriptively for each dose level or dose schedule in Part 1 and Part 3 and for each cohort in Parts 2 and 4. All abnormal findings in clinical laboratory test results, vital signs, physical examinations, echocardiograms, and ECGs will be listed. **Efficacy:** All efficacy assessments, including ORR, BOR, TTR, DOR, CBR, and PFS will be based on RECIST 1.1. The ORR based on the Investigator's assessment will be the primary efficacy endpoint and will be summarized for each cohort in Parts 1, 2, 3 and 4 and for each tumor type in Parts 2 and 4 using the response evaluable population. ORR based on an independent radiology review will also be assessed. The BOR will be summarized similarly. The TTR will be summarized by descriptive statistics. The DOR will be summarized for tumor type in Part 2 using the Kaplan-Meier method for patients with CR or PR as BOR. The OS and PFS will be summarized for tumor type in Parts 2, 3, and 4 by the Kaplan-Meier method using all treated patients. Efficacy assessments based on irRECIST will be evaluated. Pharmacokinetic parameters will be tabulated and summarized with descriptive statistics. Values for biomarker expression will be calculated at each observation time. Changes in expression from screening to each observation time will be assessed.

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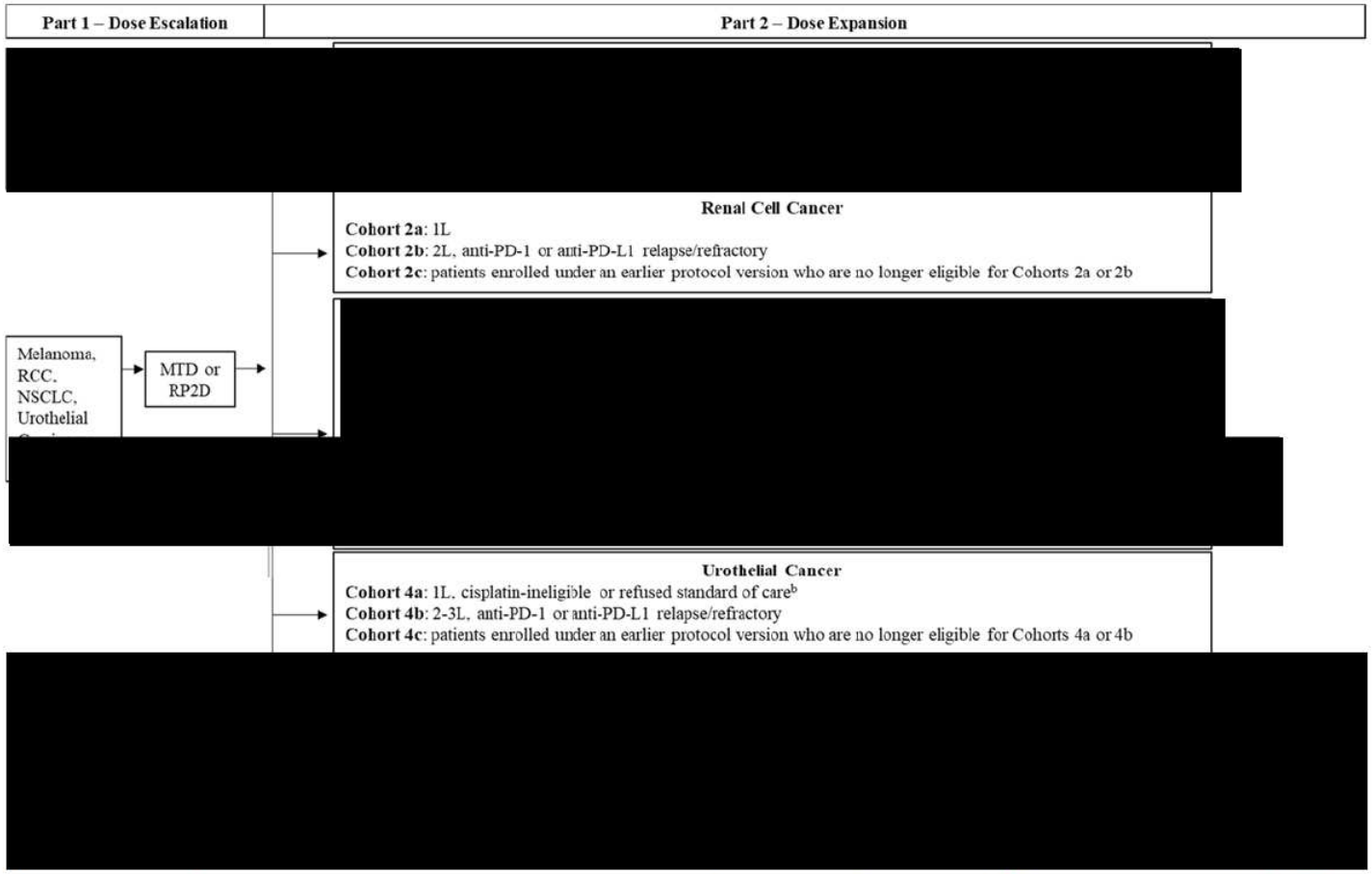
1.1 Study Schematics

Figure 1: Study Schematic for Parts 1 and 2



Abbreviations: 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; SCLC = small-cell lung cancer; SOC = standard of care; TNBC = triple-negative breast cancer

a. Up to 20 NSCLC patients will be enrolled in each cohort of PD-L1 negative, PD-L1 low/intermediate, or PD-L1 positive.

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.

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Figure 2: Study Schematic for Parts 3 and 4

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1.2 Schedule of Events

Table 1: Schedule of Events for Parts 1 and 3

Assessment Period	Screening	Cycle 1 Only							Cycle 2 and Beyond		Post-treatment	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 11**	**Day 1**	**Day 8[u]**	**End of Treatment[v]**	**Follow up 3 mo[w]**
Physical examination[b]	X	X	X	X			X		X		X	
Vital signs[c]	X	X[c]	X[c]	X[c]			X	X	X[c]	X	X	
ECOG performance status	X								X			
ECG[d]	X	X		X		Part 1 only	X	Part 1 only				
ECHO/MUGA[e]	X										X	
Pregnancy test[f]	X	X							X		X	
Hematology[g]	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[h]	X	X			X		X	X	X	X	X	
Coagulation[h]	X	X			X		X	X	X	X	X	
Additional labs [i]	X							X	X[i]		X	
Urinalysis (dipstick)[j]	X	X							X		X	
Serology[h]	X											
Archival tumor tissue[k]	X											
Tumor biopsy[l]	X								X[o]		X[o]	

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Table 1: Schedule of Events for Parts 1 and 3 (Contd)

Assessment Period	Screening	Cycle 1 Only							Cycle 2 and Beyond		Post-treatment	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 11**	**Day 1**	**Day 8[u]**	**End of Treatment[v]**	**Follow up 3 mo[w]**
Immunogenicity serum sample[m]		X							X		X	X
Complement activation sample[m]		X										
Tumor assessment[n]	X								Every 8 weeks (± 7d)		X	X
Biomarker blood sample[o]		X					X		X	X	X	
Stool sample collection[p]	Part 3 only								Part 3 only			
NKTR-214 PK blood sample[q]		X	X	X	Part 1 only	Part 1 only	X	Part 1 only	X	X		
Nivolumab or ipilimumab PK blood sample[q]		X							X			
BRAF mutation testing[r]	Part 3 only											
Administer IV fluids[s]		X	X						X			
Drug administration[t]		X							X			
Long-term follow-up[u]												X

Footnotes:

a. The acceptable visit window is ± 3 days for Day 1. Cycle intervals less than 21 days (e.g., 21 days minus-3 days) should only occur if the investigator believes there are no safety concerns with dosing the patient 1 to 3 days prior to a 21-day cycle. Additional visit windows are: ± 2 days for Day 8 in Cycle 2 and beyond; ± 7 days for the follow-up visits post-treatment and + 10 days for End of Treatment (EOT) visit at 30 days. Visits may be skipped or postponed if prospectively identified by the Investigator (e.g., national holidays, patient holidays). If Day 4 visit is missed, then Day 4 assessments must be done at the next in-clinic visit. All procedures and examinations should be performed before the administration of study drug(s), except as indicated.

b. See Section 7.13.

c. Some clinic visits will have more frequent vital sign measurements. See Appendix 2 Schedule of Assessments and Sections 5.3.7.1 and 7.14.

d. See Section 7.15. In Cycle 1 only, ECGs are performed prior to each NKTR-214 PK sampling time (see Appendix 2 Schedule of Assessments for PK and ECG sampling times). The frequency of ECGs may be increased if clinically indicated.

e. A standard echocardiogram or MUGA will be performed for all patients within 60 days prior to dosing Cycle 1 Day 1 and at EOT to assess for cardiac function and left ventricular ejection fraction (LVEF). See Section 7.16.

f. See Section 7.17.

g. Hematology assessments scheduled for the day of study drug(s) dosing must be available and assessed before dosing. The sampling for hematology assessments can be drawn within 72 hours prior to dosing. See Appendix 1.

h. The sampling for laboratory tests can be drawn within 72 hours prior to dosing. See Appendix 1.

i. Additional tests performed by local laboratory at Screening, on Day 11 of Cycle 1 for Parts 1 and 3, on Day 1 beginning from Cycle 4, and at EOT (Appendix 1). The sampling for additional tests can be drawn within 72 hours prior to dosing.

j. Microscopy is required only to follow-up clinically significant urine dipstick findings (Appendix 1).

k. Unstained formalin-fixed, paraffin embedded, archival tumor tissue sections on slides are acceptable, see Section 5.10.2 for additional details.

l. Unstained FFPE embedded, tumor tissue sections on slides (≥ 20) or FFPE embedded tumor tissue blocks from a recent biopsy collected within 6 months prior to Cycle 1 Day 1 and without intervening therapy, are acceptable in lieu of a fresh tumor biopsy prior to treatment. See Section 5.10.2.

m. See Section 5.9 and Appendix 2 Schedule of Assessments.

n. Tumor assessment at Screening then every 8 weeks (± 7 days) from Cycle 1 Day 1 and EOT (unless scan done within 4 weeks) (Section 5.7). Assessments will become less frequent during the long-term follow-up period (Section 5.5). Confirmation of tumor response is discussed in Section 8.2.2.3.

o. See Section 5.10.1 and Appendix 2 Schedule of Assessments. Optional tumor biopsies should be collected at least 30 days after Cycle 1 Day 1 but prior to the Week 8 scan and at suspected or known disease progression; collect an additional biomarker blood sample at the same time. Based on on-going biomarker analysis, samples may be taken at different time points or stopped.

p. See Section 5.10.3.

q. See Section 5.8 and Appendix 2 Schedule of Assessments. In the event of a possible study drug(s)-related serious adverse event (SAE) throughout the study, additional PK blood samples may be drawn as close to the event as possible to help characterize any possible relationships between drug exposure and the clinical event.

r. (Melanoma patients only): BRAF mutation test sample must be submitted for testing prior to Cycle 1 Day 1, if local BRAF status is unknown.

s. See Section 5.3.7.2.

t. Cycle dosing is defined based on the NKTR-214 dose schedule. See Section 5.3 for additional details.

u. See Section 5.5.

v. See Section 5.4.

w. See Section 5.5.

Abbreviations: d = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; MUGA = multigated acquisition; PK = pharmacokinetic.

Table 2: Schedule of Events for Parts 2 and 4

Assessment Period	Screening	Cycle 1 Only				Cycle 2 and Beyond		Post-treatment	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 1**	**Day 8[u]**	**End of Treatment[v]**	**Follow up 3 mo[w]**
Physical examination[b]	X	X			X	X		X	
Vital signs[c]	X	X[c]	X[c]	X[c]	X	X[c]	X	X	
ECOG performance status	X					X			
ECG[d]	X	X		X	X				
ECHO/MUGA[e]	X							X	
Pregnancy test[f]	X	X				X		X	
Hematology[g]	X	X	X	X	X	X	X	X	
Serum chemistry[h]	X	X			X	X	X	X	
Coagulation[h]	X	X			X	X	X	X	
Additional labs [i]	X					X[i]		X	
Urinalysis (dipstick)[j]	X	X				X		X	
Serology[h]	X								
Archival tumor tissue[k]	X								
Tumor biopsy[l]	X					X[o]		X[o]	

Table 2: Schedule of Events for Parts 2 and 4 (Contd)

Assessment Period	Screening	Cycle 1 Only				Cycle 2 and Beyond		Post-treatment	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 1**	**Day 8[u]**	**End of Treatment[v]**	**Follow up 3 mo[w]**
Immunogenicity serum sample[m]		X				X		X	X
Complement activation sample[m]		X							
Tumor assessment[n]	X					Every 8 weeks (± 7d)		X	X
Biomarker blood sample[o]		X			X	X	X	X	
Stool sample collection[p]	X					X			
NKTR-214 PK blood sample[q]		X		X	X	X	X		
Nivolumab or ipilimumab PK blood sample[q]		X				X			
BRAF mutation testing[r]	X								
Administer IV fluids[s]		X	X			X			
Drug administration[t]		X				X			
Long-term follow-up[u]									X

Footnotes:

a. The acceptable visit window is ± 3 days for Day 1. Cycle intervals less than 21 days (e.g., 21 days minus-3 days) should only occur if the investigator believes there are no safety concerns with dosing the patient 1 to 3 days prior to a 21-day cycle. Additional visit windows are: ± 2 days for Day 8 in Cycle 2 and beyond; ± 7 days for the follow-up visits post-treatment and + 10 days for End of Treatment (EOT) visit at 30 days. Visits may be skipped or postponed if prospectively identified by the Investigator (e.g., national holidays, patient holidays). If Day 4 visit is missed, then Day 4 assessments must be done at the next in-clinic visit. All procedures and examinations should be performed before the administration of study drug(s), except as indicated.

b. See Section 7.13.

c. Some clinic visits will have more frequent vital sign measurements. See Appendix 2 Schedule of Assessments and Sections 5.3.7.1 and 7.14.

d. See Section 7.15. In Cycle 1 only, ECGs are performed prior to each NKTR-214 PK sampling time (see Appendix 2 Schedule of Assessments for PK and ECG sampling times). The frequency of ECGs may be increased if clinically indicated.

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e. A standard echocardiogram or MUGA will be performed for all patients within 60 days prior to dosing Cycle 1 Day 1 and at EOT to assess for cardiac function and left ventricular ejection fraction (LVEF). See Section 7.16.

f. See Section 7.17.

g. Hematology assessments scheduled for the day of study drug(s) dosing must be available and assessed before dosing. The sampling for hematology assessments can be drawn within 72 hours prior to dosing. See Appendix 1.

h. The sampling for laboratory tests can be drawn within 72 hours prior to dosing. See Appendix 1.

i. The sampling for additional tests can be drawn within 72 hours prior to dosing.

j. Microscopy is required only to follow-up clinically significant urine dipstick findings (Appendix 1).

k. Unstained formalin-fixed, paraffin embedded, archival tumor tissue sections on slides are acceptable, see Section 5.10.2 for additional details.

l. Unstained FFPE embedded, tumor tissue sections on slides (≥ 20) or FFPE embedded tumor tissue blocks from a recent biopsy collected within 6 months prior to Cycle 1 Day 1 and without intervening therapy, are acceptable in lieu of a fresh tumor biopsy prior to treatment. See Section 5.10.2.

m. See Section 5.9 and Appendix 2 Schedule of Assessments.

n. Tumor assessment at Screening then every 8 weeks (± 7 days) from Cycle 1 Day 1 and EOT (unless scan done within 4 weeks) (Section 5.7). Assessments will become less frequent during the long-term follow-up period (Section 5.5). Confirmation of tumor response is discussed in Section 8.2.2.3.

o. See Section 5.10.1 and Appendix 2 Schedule of Assessments. Optional tumor biopsies should be collected at least 30 days after Cycle 1 Day 1 but prior to the Week 8 scan and at suspected or known disease progression; collect an additional biomarker blood sample at the same time. Based on on-going biomarker analysis, samples may be taken at different time points or stopped.

p. See Section 5.10.3.

q. See Section 5.8 and Appendix 2 Schedule of Assessments. In the event of a possible study drug(s)-related serious adverse event (SAE) throughout the study, additional PK blood samples may be drawn as close to the event as possible to help characterize any possible relationships between drug exposure and the clinical event.

r. (Melanoma patients only): BRAF mutation test sample must be submitted for testing prior to Cycle 1 Day 1, if local BRAF status is unknown.

s. See Section 5.3.7.2.

t. Cycle dosing is defined based on the NKTR-214 dose schedule. See Section 5.3 for additional details.

u. See Section 5.5.

v. See Section 5.4.

w. See Section 5.5.

Abbreviations: d = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; MUGA = multigated acquisition; PK = pharmacokinetic.

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2.0 INTRODUCTION

2.1 Background

2.1.1 NKTR-214 Mechanism of Action

Aldesleukin (recombinant human interleukin-2 [rhIL-2]) directly stimulates the immune system and has been shown to lead to durable responses in ~10% of people with metastatic melanoma and renal cancer (Payne, 2014). However, in addition to aldesleukin acting as a stimulator of the immune system by activating tumor killing CD8+ T cells, it also suppresses the immune system by activating regulatory T (Treg) cells (Boyman, 2012). Despite favorable clinical outcomes associated with aldesleukin, it has several therapeutic limitations including the need for inpatient hospital administration, 5 consecutive days of dosing, and the potential for serious toxicities, comprising capillary leak syndrome, hypotension, and pulmonary edema requiring medical management in the intensive care unit. In contrast to aldesleukin, NKTR-214 was designed as an outpatient therapy. In addition, NKTR-214 was designed to mitigate the serious toxicities associated with rapid systemic immune activation seen with administration of high-dose interleukin-2 (IL-2).

NKTR-214, a novel cytokine with enhanced immune system activation and the targeted profile of NKTR-214 (i.e., a superior safety profile allowing for outpatient administration and a longer duration of action requiring less frequent dosing) has the potential to be an important advancement for the treatment of patients with cancer. NKTR-214 consists of IL-2, which has the same amino acid sequence as aldesleukin, conjugated at a defined region within the protein to releasable polyethylene glycol (PEG) chains. The PEG chains render the molecule inactive. After administration in vivo, the PEG chains are slowly hydrolyzed to generate active cytokine conjugates. The most active IL-2 conjugates are 2-PEG-IL2 and 1-PEG-IL2. The location of the PEG chains on the active conjugated-IL-2 reduces its affinity to the IL-2 receptor alpha subunit (IL2Rα), responsible for activating undesirable Treg cells to a greater extent than affinity to the IL-2-receptor beta subunit (IL2Rβ). In the tumor, NKTR-214 preferentially activates CD8+ T cells and natural killer (NK) cells over Treg cells and provides sustained exposure to active 1-PEG and 2-PEG-IL2.

2.1.2 Rationale for the Combination of NKTR-214 and Immune Checkpoint Inhibitors

Accumulating evidence suggests that patients with low baseline CD8+ T cells within the tumor microenvironment (tumor infiltrating lymphocytes [TILs]) predict poor response to checkpoint inhibitor immunotherapies (Daud, 2016a; Daud, 2016b); thus, agents designed to specifically activate and expand CD8+ T cells may improve clinical outcomes in patients with low TILs. NKTR-214 targets the IL-2 pathway and is designed to provide biased sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rβɣ) to preferentially activate and expand NK and effector CD8+ T cells over Treg cells. Preliminary analyses of patients' blood and tumor by flow cytometry and immunohistochemistry (IHC) demonstrate that NKTR-214, as a single agent, increases activated CD4+ and CD8+ T cells in peripheral blood, with an increase in

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T cell infiltrates within the tumor tissue after 1 dose of NKTR-214. In addition, there is an increase in programmed cell death receptor-1 (PD-1) expression on T cells in the blood and tumor after treatment with NKTR-214. The ability to alter the immune environment and increase PD-1 expression on effector T cells may improve the effectiveness of anti-PD-1 blockade.

2.1.3 Clinical Experience with IL-2 and Checkpoint Inhibitors

Simultaneous administration of IL-2 with immune checkpoint inhibitors directed against PD-1 (nivolumab and pembrolizumab) or its ligand has not been reported as of the date of this protocol, although several studies are ongoing in which IL-2 and an anti-PD-1 antibody are co-administered following an infusion of either adoptive CD8+ T cells or tumor-infiltrating lymphocytes (NCT02757391, NCT02500576).

Published data on the sequential administration of IL-2 with an anti-PD-1 inhibitor have been reported recently. A case report noted a near-complete response (near-CR) with extended duration of response when a patient with renal cell carcinoma (RCC; non-responsive to nivolumab) was treated with high-dose IL-2 (Brayer, 2014). A larger experience from an observational clinical trial reported that patients with metastatic melanoma who received high-dose IL-2 and received either ipilimumab or an anti-PD-1 inhibitor experienced a differential increase in median overall survival, 15.8 vs 28.7 months, respectively. The 12-month survival rate was 64% for patients receiving ipilimumab post high-dose IL-2 compared with 97% for patients receiving an anti-PD-1 inhibitor, suggesting that these two checkpoint inhibitors do not have overlapping mechanisms of action and that IL-2 may enhance the curative potential of the anti-PD-1 inhibitor (Wong, 2015). In support of the hypothesis that IL-2 may have enhanced the curative potential of nivolumab/pembrolizumab, a recent report demonstrated that IL-12, which has been shown to induce tumor infiltrating lymphocytes and anti-tumor immunity similar to IL-2, appeared to prime response to anti-PD-1/PD-L1 inhibitors and demonstrated a clinical benefit rate of 75% (50% CR and 25% partial response [PR]) (Algazi, 2016).

2.1.4 Clinical Experience with NKTR-214

Study 15-214-01 (NCT02869295) is a Phase 1/2 open-label, multicenter, dose escalation and dose expansion monotherapy study of NKTR-214 in patients with locally advanced or metastatic solid tumors. The objectives of the study are to evaluate the safety and tolerability of NKTR-214 to determine the maximum tolerated dose (MTD) as well as to assess the objective response rate (ORR) at or below the MTD, or to identify the recommended Phase 2 dose (RP2D).

In Study 15-214-01, hypotension has been identified as a principal toxicity. Hypotension is a known adverse event (AE) associated with both IL-2 and engineered cytokines. Instances of hypotension most commonly appeared 2-3 days following the first infusion, coinciding with the peak plasma concentration of the active metabolites formed after administration of NKTR-214. Patients for whom intravenous (IV) fluid administration was clinically indicated responded

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rapidly (in less than 24 hours) to IV hydration. To mitigate the risk of hypotension, management guidelines were implemented and included the following recommendations:

- Discontinuation of antihypertensive therapy and drugs with hypotensive properties, prior to administration of NKTR-214.
- Maintaining adequate oral fluid intake, particularly during the first 5 days post-dose.
- Avoiding activities that could lead to dehydration (e.g., physically strenuous activity) or vasodilation (e.g., hot showers, sauna).
- Providing additional corticosteroid support for patients with adrenal insufficiency on corticosteroid replacement therapy.

Since the implementation of these mitigation measures, the frequency of hypotension, particularly Grade 3 hypotension, has been reduced.

In contrast to aldesleukin, none of the 28 patients treated to date with NKTR-214 monotherapy have experienced capillary leak syndrome. In addition, the severity and duration of any temporally associated hypotension is markedly reduced. The most common Grade 1-2 treatment-related AEs were fatigue, pruritus, chills, and decreased appetite. Grade 3 treatment-related AEs included hypotension, abdominal pain, and infusion-related reaction. For the every 3 weeks (q3w) dosing frequency, NKTR-214 monotherapy doses up to 0.009 mg/kg were well tolerated. At 0.012 mg/kg NKTR-214 monotherapy dose, one patient experienced DLTs of Grade 3 hypotension and syncope, which was rapidly reversed with fluids; this patient received another 2 doses at a lower dose of 0.006 mg/kg and tolerated treatment well. Dosing at 0.006 mg/kg q2w and q3w, as well as dosing at 0.003 and 0.009 mg/kg at q3w of NKTR-214 monotherapy have been deemed safe per the Safety Review Committee. No Grade 4 treatment-related AEs were reported. One patient dosed at 0.009 mg/kg discontinued the study due to a treatment-related AE of infusion-related reaction. The pattern of AEs attributable to NKTR-214 observed in Study 15-214-01 is dissimilar from the immune-mediated AEs (imAEs) that commonly develop with the use of checkpoint inhibitors. Neither clinical nor nonclinical data predict "immune-mediated inflammatory events," such as endocrinopathies, colitis, nephritis, pneumonitis, dermatitis, or hepatitis to occur with NKTR-214. The non-overlapping toxicities observed with NKTR-214 and nivolumab may therefore result in a reasonably well-tolerated immuno-oncology combination.

Additional details on the clinical experience with NKTR-214 are provided in the NKTR-214 Investigator's Brochure.

2.1.5 Flat Dose Regimens with Nivolumab (360 mg q3w and 480 mg q4w)

Currently nivolumab is being studied at a flat 360 mg q3w and/or 480 mg q4w dose schedule in a number of clinical trials:

Phase 3: NSCLC, NCT02864251, NCT02713867

Phase 2: NSCLC, NCT02967133, NCT03041181, NCT02434081

Phase 2: RCC, NCT02959554

Population pharmacokinetic (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. As the PK of nivolumab is linear, the corresponding flat dose for a every 3 weeks (q3w) dosing regimen is nivolumab 360 mg. Using the PPK model developed, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 360 mg administered q3w. The simulated steady-state average concentration (C_{avgss}) following administration of nivolumab 360 mg q3w are expected to be similar to those following administration of nivolumab 3 mg/kg every 2 weeks (q2w) to patients weighing 80 kg, the approximate median weight of patients used in the PPK analyses. The predicted steady state peak (C_{maxss}) concentrations following nivolumab 360 mg q3w are predicted to be less than those following the administration of nivolumab 10 mg/kg q2w providing sufficient safety margins.

Nivolumab 480 mg administered every 4 weeks (q4w) is also currently under investigation. The less frequent dosing schedule is designed to be more convenient for patients. The 480 mg dose was chosen based on clinical data as well as modeling and simulation approaches using PPK and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small cell lung cancer [NSCLC], and RCC) to provide an approximately equivalent dose as 3 mg/kg q2w. Exposures with the 480 mg q4w regimen are predicted to be within the exposure ranges observed at doses up to 10 mg/kg q2w assessed in the nivolumab clinical program and, therefore, are not considered to cause an increased risk to patients.

Based on these supportive data, nivolumab 360 mg q3w will be examined in the current study with NKTR-214.

Additional details are provided in the nivolumab Investigator's Brochure.

2.1.6 Nivolumab Shorter Infusion Duration

Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration, and nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across the nivolumab clinical program. In study CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All of the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the 10 mg/kg dose) is not expected to present any safety concerns based on the prior experience of 10 mg/kg infused over 60 minutes. The safety of 3 mg/kg nivolumab administered as a 30-minute infusion was assessed in CA209153 in patients (n = 322) with previously treated

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advanced NSCLC. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment related) between patients infused over 30 minutes versus the frequency reported for 60-minute infusions. Thus, nivolumab is considered safe to infuse over 30 minutes.

Additional details are provided in the nivolumab Investigator's Brochure.

2.1.7 Nivolumab Safety Summary

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 patients treated to date.

For monotherapy, the safety profile is similar across tumor types. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and is manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and by timely immunosuppressive therapy or other supportive care.

In several ongoing clinical studies, the safety of nivolumab in combination with other therapeutics is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab + ipilimumab, which is approved in patients with unresectable or metastatic melanoma, and is being investigated in multiple other tumor types. Results to date suggest that the safety profile of nivolumab + ipilimumab combination therapy is consistent with the mechanisms of action of each drug. The nature of the AEs is similar to that observed with either agent as a monotherapy; however, the frequency and severity of most AEs are increased with combination therapy.

Additional details on the safety profile of nivolumab are provided in the nivolumab Investigator's Brochure.

2.1.8 Ipilimumab Shorter Infusion Duration

[redacted]

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[redacted]

2.1.9 Ipilimumab Safety Summary

[redacted]

2.1.10 Safety Summary of Study Regimen in Patients with 1L Nonsquamous NSCLC

[redacted]

2.1.11 Safety Summary of Paclitaxel Formulations in Patients with 1L NSCLC

[redacted]

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[redacted]

2.1.12 Safety Summary of Nab-Paclitaxel in Patients with TNBC

[redacted]

[redacted]

2.1.13 Safety Summary of Eribulin in Patients with TNBC

[redacted]

[redacted]

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[redacted]

2.2 Overall Benefit/Risk

NKTR-214 was designed to mitigate the serious toxicities associated with rapid systemic immune activation seen with administration of aldesleukin. The goal of engineering a PEGylated form of IL-2 that reduces the treatment-limiting toxicities of aldesleukin, i.e., those necessitating in-hospital administration, appears to have been realized with NKTR-214 at the doses tested. The safety profiles of nivolumab and ipilimumab are well characterized and manageable when administered alone or in combination, including regimens where they are administered in combination with additional immuno-oncology products. Nonclinical data as well as clinical experience with high-dose IL-2 and checkpoint inhibitor combinations indicate the potential for improvement in therapeutic response compared with either agent given alone. Thus, the potential benefit of combination therapy appears to outweigh the known risks of these agents and warrants clinical investigation.

2.3 Data Monitoring Committee

The detailed and frequent safety monitoring that will be undertaken in this open-label study precludes the necessity for an independent Data Monitoring Committee. A separate Safety Review Committee will meet to review safety data (see Section 9.3).

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3.0 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the safety and tolerability, and define the MTD and/or 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

3.2 Secondary Objectives

The secondary objective of this study is:

- 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)

3.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate the efficacy of NKTR-214 in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies by assessing immune-related RECIST (irRECIST) at the RP2D
- To assess the immunological effects in blood and the tumor environment, and to measure disease-specific pharmacodynamics markers such as lactate dehydrogenase (LDH) (e.g., in melanoma), of NKTR-214 when administered in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies
- To characterize the pharmacokinetics (PK) of nivolumab, ipilimumab, NKTR-214, and NKTR-214 metabolites when NKTR-214 is administered in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies.
- To assess the development of anti-drug antibodies against NKTR-214, nivolumab, and ipilimumab when NKTR-214 is administered in combination with nivolumab or in combination with nivolumab and other anti-cancer therapies.
- To assess the association between efficacy measures and PD-L1 expression in tumors, tumor and blood-based mutational burden, and inflammation status when NKTR-214 is administered in combination with nivolumab and in combination with nivolumab and other anti-cancer therapies

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4.0 SELECTION OF STUDY POPULATION

For the purposes of patient eligibility determination, note the following definitions:

- For the purposes of eligibility, "neoadjuvant therapy" is defined as systemic chemotherapy administered prior to definitive local surgery in a patient without distant metastases; "adjuvant therapy" is defined as systemic therapy administered following definitive local therapy (surgery or radiation) in a patient without distant metastases (with no evidence of disease).
- A "line of therapy" is defined as any regimen – single-agent or combination therapy, cytotoxic therapy, immuno-oncology therapy separately or in combination – that is given for patients with advanced disease, and that is stopped for any reason, including progression of disease, toxicity, physician decision, or patient withdrawal of consent.

4.1 Inclusion Criteria

Each patient will be entered into this study only if he/she meets all of the following criteria:

For Dose Escalation (Part 1), Dose Expansion (Part 2), and Parts 3 and 4 (For Triplet Combination):

1. Provide written, informed consent to participate in the study and follow the study procedures
2. Male or female patients, age 18 years or older at the time of signing the informed consent form (ICF)
3. Life expectancy >12 weeks
4. Patients must not have received prior interleukin-2 (IL-2) therapy.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
6. Measurable disease per RECIST 1.1
7. Demonstrated adequate organ function, as defined below, within 28 days of treatment initiation
    a. White blood cell (WBC) count ≥ 2000/μL (after at least 7 days without growth factor support)
    b. Absolute neutrophil count (ANC) ≥ 1500/μL (after at least 7 days without growth factor support)
    c. Platelet count ≥ 100×10^3/μL (no transfusions allowed within 7 days of Cycle 1 Day 1 to meet entry criteria)

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d. Hemoglobin ≥ 9.0 g/dL (no transfusions allowed within 7 days of Cycle 1 Day 1 to meet entry criteria)

e. Serum creatinine ≤ 2 mg/dL (or glomerular filtration rate ≥ 40 mL/min); patients with urothelial carcinoma who are cisplatin ineligible (creatinine clearance < 60 mL/min) may be enrolled if the glomerular filtration rate is ≥ 30 mL/min.

f. Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤ 3× upper limit of normal (ULN)

g. Total bilirubin within normal limits (total bilirubin ≤ 2× ULN if associated with hepatobiliary metastases or Gilbert's syndrome)

h. Lipase and amylase ≤ 1.5× ULN. Patients with pancreatic metastases and lipase and/or amylase < 3× ULN may enroll. Patients may not enroll if there are clinical or radiographic signs of pancreatitis.

8. A documented left ventricular ejection fraction (LVEF) > 45% using standard echocardiogram or multigated acquisition (MUGA) scan test within 60 days prior to Cycle 1 Day 1.

9. Oxygen saturation ≥ 92% on room air

10. Clinically significant toxic effect(s) of the most recent prior anti-cancer therapy must be Grade 1 or resolved (except alopecia and sensory neuropathy); patients with Grade 2 adrenal insufficiency related to prior anti-cancer therapy (defined as requiring medical intervention, such as concomitant steroids) or Grade 2 hypothyroidism (defined as requiring hormone replacement therapy) may be enrolled provided that clinical symptoms are adequately controlled and the daily dose is 10 mg or less of prednisone or equivalent. If the patient received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

11. Women of childbearing potential (WCBP) must agree and commit to the use of highly effective methods of birth control throughout the duration of the study until 6 months following the last dose of study drug. Acceptable methods are defined as those that result, alone or in combination, in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as surgical sterilization, an intrauterine device, or hormonal contraception in combination with a barrier method. It is currently unknown whether NKTR-214 may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add a barrier method. In certain countries (if permitted by law), WCBP may agree to abide by heterosexual sexual abstinence during the time of participation in this study.

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12. Male patients and their female partners of childbearing potential must agree and commit to use a double-barrier contraception (e.g., condom with spermicidal foam/gel/film/cream/suppository) throughout the duration of the study until 6 months following the last dose of study drug; in addition to their female partner using either an intrauterine device or hormonal contraception and continuing until 6 months following the last dose of study drug. This criterion is not applicable for male patients who have had a vasectomy > 6 months before signing the informed consent form (ICF).

13. Patients must not have active brain metastases:

    a. Participants with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study treatment administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study treatment administration. Stable dose of anticonvulsants is allowed. Treatment for CNS metastases may include stereotactic radiosurgery (e.g. GammaKnife, CyberKnife, or equivalent) or neurosurgical resection. Patient who received whole brain radiation therapy are not eligible.

    b. No new or progressing brain metastasis of any size

    c. No stereotactic radiation or craniotomy within 4 weeks of Cycle 1 Day 1

    d. No new central nervous system lesions on repeat radiographic imaging 4 weeks or more from last treatment

    e. No clinically significant symptoms secondary to brain metastases

    f. Head imaging must occur on study in accordance with Section 5.7.

14. Sample of fresh baseline tumor biopsies (fresh baseline biopsy is defined as a biopsy specimen taken during screening) is required, except if inaccessible and with Medical Monitor approval (e.g., a biopsy specimen from a sample taken since completion of the most recent prior systemic treatment and no longer than 6 months prior to study start may be acceptable in lieu of a fresh biopsy with Medical Monitor approval). Patients must also consent to allow acquisition of existing formalin-fixed paraffin-embedded (FFPE) material (archival tumor tissue), either a block or unstained slides for performance of correlative studies.

For Parts 1 and 2

For Disease-Specific Tumor Types

15. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]

Cohort 1b − [redacted]

a. [redacted]

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b. [redacted]

[redacted]

[redacted]

[redacted]

Cohort 1c – [redacted]

a. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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Cohort 1d – [redacted]

- [redacted]
- [redacted]

Cohort 1e – [redacted]

- [redacted]

16. Renal Cell Carcinoma (RCC)

    a. Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC stage IV) RCC

    b. Histologically confirmed RCC with a clear-cell component

Cohort 2a – RCC (1L)

a. Have not received prior anti-cancer therapy for advanced or metastatic RCC.

b. Prior to disease metastasis, patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens, including, but not limited to, checkpoint inhibitors such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) antibody, or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways, indoleamine 2,3-dioxygenase pathway inhibitors, cancer vaccines, adoptive cell therapies, or other cytokine therapies.

[redacted]

- [redacted]

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b. [redacted].

[redacted]

[redacted]

17. Non-Small Cell Lung Cancer (NSCLC)

a. [redacted]

[redacted]

[redacted]

[redacted]

b. [redacted]

[redacted]

[redacted]

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b. [redacted]

[redacted]

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[redacted]

[redacted]

[redacted]

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b. [redacted]

[redacted]

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[redacted]

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c. [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

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- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

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18. Urothelial Carcinoma

a. Histologically or cytologically documented locally advanced or transitional cell carcinoma of the urothelium including renal pelvis, ureters, urinary bladder, or urethra. Patients with mixed histologies are required to have a dominant transitional cell pattern.

Cohort 4a − Urothelial Carcinoma (1L)

a. Enrollment of urothelial carcinoma 1L patients will target accrual of up to 20 patients who are cisplatin-ineligible and up to 20 patients, who, after consultation with the Investigator, choose to forego front-line chemotherapy.

b. Treatment naive patients who refuse chemotherapy standard of care or treatment naive, cisplatin-ineligible patients who meet at least one of the following criteria:

- Creatinine clearance (calculated or measured) < 60 mL/min. Cisplatin-ineligible patients must have a creatinine clearance < 60 mL/min and GFR ≥ 30 mL/min.
- Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade ≥ 2 audiometric hearing loss
- CTCAE v4.03 Grade ≥ 2 peripheral neuropathy

c. No prior chemotherapy for inoperable locally advanced or metastatic urothelial carcinoma. Prior local intravesical chemotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment.

d. For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval of more than 12 months between the last treatment administration and the date of recurrence is required to be considered treatment naive in the metastatic setting. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

[redacted]

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c. [redacted]

[redacted]

[redacted]

[redacted]

[redacted].

19. Cohort 5 − Triple-Negative Breast Cancer (1-2L, I-O therapy naive)

a. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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e. [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

- [redacted]

[redacted]

- [redacted]

- [redacted]

[redacted]

- [redacted]

20. Cohort 6 – Hormone-Receptor Positive, HER2 Negative Breast Cancer

a. [redacted]

- [redacted]
- [redacted]
- [redacted]

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b. [redacted]

[redacted]

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21. Cohort 7 − Gastric Carcinoma (2-3L, I-O therapy naive)

a. [redacted]

- [redacted]
- [redacted]
- [redacted]

22. Cohort 8a – Colorectal Carcinoma (2-3L+, I-O therapy naive); microsatellite instability (MSI)-high

a. [redacted]

- [redacted]

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c. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

c. [redacted]

[redacted]

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[redacted]

23. **Cohort 9 –Small Cell Lung Cancer (2L, I-O therapy naive)**

a. [redacted]

- [redacted]
- [redacted]

For Parts 3 and 4 (NKTR-214/nivolumab/ipilimumab)

[redacted]

24. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

25. [redacted]

- [redacted]

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- [redacted]
- [redacted]

26. [redacted]

  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

27. [redacted]

- [redacted]

[redacted]

b. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.2 Exclusion Criteria

A patient will be excluded from this study if he/she meets any of the following criteria:

1. Use of an investigational agent or an investigational device within 28 days before administration of first dose of study drug

2. Females who are pregnant or breastfeeding

3. Patients who have an active, known or suspected autoimmune disease. Patients requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease that requires systemic steroids or immunosuppressive agents. (Exceptions include any patient on 10 mg or less of prednisone or equivalent, patients with vitiligo, hypothyroidism stable on hormone replacement, Type I diabetes, Graves' disease, Hashimoto's disease, alopecia areata, eczema, or with Medical Monitor approval.)

4. History of allergy or hypersensitivity to study drug components

5. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer. An incidental finding of prostate cancer (identified upon resection of the prostate) is acceptable, provided that the following criteria are met: Stage T2N0M0 or lower; Gleason score ≤ 6, and prostate-specific antigen (PSA) below lower limit of normal by local laboratory.

6. History of organ or tissue transplant that requires systemic use of immune suppressive agents

7. Evidence of clinically significant interstitial lung disease or active, noninfectious pneumonitis

8. Prior surgery or radiotherapy within 14 days of therapy. Patients must have recovered from all radiation-related toxicities, and not require corticosteroids.

9. Patients who have had < 28 days since the last chemotherapy, biological therapy, or < 14 days from approved tyrosine kinase inhibitor (TKI) therapy (sunitinib, sorafenib, vemurafenib, dabrafenib, cobimetinib, erlotinib, gefitinib, afatinib, osimertinib), < 14 days from last dose of hormonal therapy (for patients with breast cancer) or systemic or inhaled steroid therapy at doses greater than 10 mg of prednisone or equivalent before administration of the first dose of study drug.

10. Parts 1 and 2: Patients in whom prior anti PD-1 / anti-PD-L1 therapy was intolerable and required discontinuation of treatment; Parts 3 and 4: Patients in whom prior anti PD-1 / anti-PD-L1 therapy and/or prior CTLA-4 therapy was intolerable and required discontinuation of treatment; patients who have discontinued prior checkpoint inhibitor therapy due to adrenal insufficiency that is now managed by replacement steroid therapy may be eligible for the trial upon Medical Monitor approval.

11. NSCLC patients who require supplemental oxygen

12. Uveal melanoma is excluded.

13. Active infection requiring systemic therapy

14. Has known hepatitis B virus (HBV) infection (e.g., hepatitis B surface antigen [HBsAg] reactive) or hepatitis C virus (HCV) infection (e.g., HCV ribonucleic acid [RNA] qualitative is detected)

15. Has known immunodeficiency or active human immunodeficiency virus (HIV-1/2 antibodies)

16. Prolonged Fridericia's corrected QT interval (QTcF) > 450 ms for men and > 470 ms for women at Screening

17. History of unstable or deteriorating cardiac disease or cerebrovascular disease within the previous 2 years prior to screening including, but not limited to, the following:

    a. Unstable angina or myocardial infarction

    b. Congestive heart failure (New York Heart Association [NYHA] Class III or IV)

    c. Uncontrolled clinically significant arrhythmias

    d. Prior cerebrovascular accident or transient ischemic attack.

18. Need for > 2 antihypertensive medications for management of hypertension (including diuretics)

19. Known current drug or alcohol abuse

20. Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results (e.g., a condition associated with diarrhea or acute diverticulitis).

For sites located in France only

21. Vulnerable populations described in Article L. 1121-6 of the French Public Health Code

22. Legally protected majors or majors who are unable to express their consent as described in Article L. 1121-8 of the French Public Health Code

For sites located in Italy only

23. Patients may not be enrolled if they have first-line urothelial cancer with cisplatin-eligible disease (Cohort 4a and Cohort 13a.2).

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5.0 TREATMENT PLAN

5.1 Overview

This is a Phase 1/2, open-label, multicenter 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 melanoma, RCC, NSCLC, urothelial carcinoma, triple-negative breast cancer (TNBC), hormone-receptor-positive breast cancer, gastric, colorectal, or SCLC. The study is divided into a Screening period, Treatment period, End of Treatment period, and Long-Term Follow-up period.

The NKTR-214 treatment period of the study is divided into a 21-day (q3w) cycle with associated evaluations and procedures. Treatment cycle is defined by the frequency of NKTR-214 administration (see Table 5).

Results of the assessments must be reviewed and documented before administering the first dose of the next cycle. Every effort should be made to schedule visits within the protocol-specified windows. NKTR-214 treatment period may be evaluated at different frequencies based on safety and biomarker data collected in an ongoing NKTR-214 monotherapy clinical trial (NCT02869295).

The study will be conducted in 4 parts: Part 1, Dose Escalation, Part 2, Dose Expansion (Figure 1), Part 3 (Schedule Finding for Triplet), and Part 4 (Dose Expansion of Triplet) (Figure 2). The sponsor will notify sites when individual cohorts are open for screening and when screening is closed. Certain cohorts may only open at select participating sites.

If multiple cohorts in the same tumor type are open for enrollment, the sponsor will assign the appropriate cohort (whether this is a Part 2 NKTR-214/nivolumab doublet cohort [with or without other anti-cancer therapies] or one of the dosing schedules investigating the NKTR-214/nivolumab/ipilimumab triplet in Parts 3 and 4).

All procedures are outlined in the Schedule of Events (Section 1.2).

5.2 Screening Period

Patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. For those cohorts that require assessment of PD-L1 or tumor infiltrating lymphocytes (TILs) by immunohistochemistry as part of screening procedures, an abbreviated informed consent that only permits assessment of PD-L1 status by the central laboratory may be used. If eligible, a patient must sign the full study informed consent before any other screening procedures may proceed). After signing the ICF, patients will be evaluated for entry criteria during the Screening period within 28 days before administration of study drug(s). Rescreening after screen failure will be allowed.

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For melanoma patients whose BRAF mutation status is unknown, the patient must have submitted sample(s) for BRAF status testing prior to the first administration of study drugs.

5.3 Treatment Period

Patients will be treated until disease progression, death, unacceptable toxicity, symptomatic deterioration, achievement of maximal response, the Investigator's decision to discontinue treatment, the patient decides to discontinue treatment or withdraw consent, lost to follow up, or Nektar Therapeutics decides to terminate the trial.

Patients with progressive disease (PD) per RECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator; see Section 5.3.9 for treatment beyond progression. Patients with a PR or stable disease (SD) will continue to receive NKTR-214 combination until achievement of a confirmed CR, disease progression, or intolerability to therapy. It is at the discretion of the Investigator to continue treating patients with a confirmed CR, for a maximum treatment of 2 years.

5.3.1 Administration of Study Drug

Each patient's NKTR-214 dose will be determined by the NKTR-214 dose escalation scheme and the patient's weight in kilograms. The patient's weight in kilograms will be determined before the start of each 3-week cycle. If the patient's weight is within 10% of the Cycle 1 Day 1 weight, the study drug doses do not need to be recalculated depending on institutional guidelines/preference. When administered on the same day, NKTR-214 will be administered first before nivolumab, ipilimumab, or other anti-cancer therapy. It is highly recommended that nivolumab administration start within 30 minutes after completion of NKTR-214 administration. [redacted] The safety of this shortened infusion time was investigated and demonstrated to show an acceptable tolerability profile (Momtaz, 2015 and Gassenmaier, 2018 also see Section 2.1.8).

Institutional guidelines for administration of other anti-cancer therapies should be followed in Part 2.

- NKTR-214 administered IV over 30 (± 5) minutes at a starting dose of 0.006 mg/kg q3w
- Nivolumab (anti-PD-1) administered IV over 30 minutes (± 5) minutes at either a 360 mg flat dose q3w (Parts 2, 3, and 4); [redacted]

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5.3.2 Part 1: Dose Escalation

Dose escalation is described in Table 3 and will be carried out as listed in Table 4.

The first NKTR-214 dose to be studied was determined based on a monotherapy trial with NKTR-214 (i.e., 0.006 mg/kg q3w). Once a dose escalation cohort has been evaluated for safety by a Safety Review Committee, which includes the Sponsor Medical Monitor and 1 site Investigator, the Sponsor may choose to concurrently enroll patients and dose NKTR-214 at lower dose levels and different dose schedules to assess the benefit/risk profile within the anticipated 50 patients. The sponsor may also evaluate other doses and dose schedules based on the safety findings from ongoing clinical trials.

For dose escalation cohorts, the Sponsor and at least one Investigator will jointly decide the following:

- Dose escalation to the next cohort and/or dose schedule
- RP2D
- Dose levels of NKTR-214 for a given cohort may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested

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- Decision to evaluate NKTR-214 in combination with nivolumab in additional patients at lower doses and different dose schedules to assess the benefit/risk profile within the anticipated total number of 50 patients

Table 3: Part 1: Dose Escalation Scheme

Cohort	NKTR-214	Nivolumab q2w	Nivolumab q3w
1	0.006 mg/kg q3w	240 mg	
2	0.006 mg/kg q3w		360 mg
3	0.006 mg/kg q2w	240 mg	
4	0.009 mg/kg q3w		360 mg

Table 4: Part 1: Dose Escalation Guide

Number of Patients with DLT at a Given Dose Level	Dose Escalation Decision Guide
0 out of 3	Enter 3 patients at the next higher dose level.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these additional 3 patients experience a DLT, will proceed to the next dose level. If 1 or more of this group suffers a DLT, then the dose escalation is stopped, and this dose is declared the maximally administered dose (MAD). Three additional patients will be entered at a lower dose level if only 3 patients were treated previously at that dose.
≥ 2	Dose escalation will be stopped. This dose level will be declared the MAD (highest dose administered). Three additional patients will be entered at a lower dose level if only 3 patients were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the MAD	This is the MTD. Depending on toxicity, PK and/or pharmacodynamic markers, this may also be the RP2D. At least 6 patients must be entered at the recommended dose for Phase 2.

Abbreviations: DLT = dose-limiting toxicity; MAD = maximally administered dose; MTD = maximum tolerated dose; PK = pharmacokinetics; RP2D = recommended Phase 2 dose

The dose-limiting toxicity (DLT) evaluation period for the combinations will be a minimum of 3 weeks (21 days). For example, for q2w dosing the DLT window is 2 cycles (28 days), for q3w dosing the DLT window is 1 cycle (21 days), and for q4w dosing the DLT window is 1 cycle (28 days) (Table 5). Any DLT past the DLT window is a delayed DLT.

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Table 5: Part 1: Treatment Cycle Duration and DLT Window

Dosing Schedule of NKTR-214	Cycle Definition	DLT Window
q2w	14 days	28 days
q3w	21 days	21 days
q4w	28 days	28 days

Abbreviations: DLT = dose-limiting toxicity; q2w = every 2 weeks; q3w = every 3 weeks; q4w = every 4 weeks

Patients will be enrolled in groups of at least 3 patients in each cohort for the dose escalation cohorts unless unacceptable toxicity is observed. The first patient of each escalating dose cohort will be monitored for safety and tolerability on Cycle 1, Days 1 through 5 before additional patients are dosed within the same cohort. Enrollment into a new cohort with an escalating dose of NKTR-214 cannot begin until the DLT window has elapsed since the last patient's first dose in the previous cohort.

The definition of a DLT is provided in Section 5.11. If no DLTs occur in a cohort of at least 3 patients, a new cohort of 3 patients may be treated at the next higher dose level (Table 4). If only 1 of 3 patients in a cohort experiences a DLT, that cohort will be expanded to 6 patients. If 3 patients have already been enrolled into a cohort and additional patients have signed the ICF and are undergoing the screening process, they may be enrolled to the cohort with Sponsor approval; however, these patients are not required to be included in the dose escalation decision for that cohort. If only 1 of the 6 patients experiences a DLT, then the next cohort of 3 patients may be treated at the next higher dose level. If 2 or more patients within a cohort experience DLTs, then that dose level will be above the MTD (the highest dose tested where no more than 1 of 6 patients has experienced a DLT), and new patients will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 patients. Moreover, the cohort Safety Review Committee or Sponsor may determine that inadequate information has been obtained in a cohort of 3 patients and to further understand the benefit/risk profile at a given dose level, additional patients may be enrolled.

All drug-related AEs after the DLT window will continue to be collected and evaluated by the Investigators and the Sponsor on an ongoing basis and may be taken into consideration in determining the MTD and/or RP2D. During dose escalation, patients who are withdrawn from the study during the DLT window for reasons other than occurrence of a DLT will be replaced.

Additional cohorts of up to 12 patients may be enrolled at doses deemed to be safe to more fully explore the safety, tolerability, pharmacokinetics, biomarker assessments, and preliminary efficacy of the NKTR-214 dose in combination with nivolumab. It is estimated that approximately 50 patients will be enrolled into the dose escalation phase of the study. If additional cohorts are enrolled, the sample size will increase accordingly.

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At least 1 study Investigator and the Sponsor Medical Monitor will meet and decide the RP2D regimen to be studied in Part 2 before the initiation of Part 2. The RP2D may be determined based on the MTD dose or a dose lower than MTD. The RP2D may also be determined based on a biological effect of the study drugs as determined by anti-tumor activity and immune activation. The Sponsor will amend the protocol to include the RP2D and will also communicate the RP2D via an administrative dosing letter to allow enrollment to begin, where permitted, before the protocol amendment is finalized.

5.3.3 Rationale for Recommended Phase 2 Dose for Part 2

Two data analyses of patients receiving NKTR-214 and nivolumab in Study 16-214-02 are provided in this section; the rationale for the recommended Phase 2 dose for Part 2 based on a data cut of October 05, 2017 is provided below and Section 5.3.3.1 provides updated safety and efficacy data as of February 8, 2018.

The safety of NKTR-214 as a single agent has been assessed in 5 monotherapy cohorts administered NKTR-214 q3w (22 patients) at doses ranging from 0.003 mg/kg to 0.012 mg/kg; a dosing frequency of q2w (6 patients) was further explored at 0.006 mg/kg (Table 6 and see Clinical Experience with NKTR-214 in Section 2.1.4). The safety of NKTR-214 in combination with nivolumab at doses shown in Table 6 has been assessed in 38 patients.

Table 6: Patient Exposure Supporting the RP2D

	NKTR-214 Dosing Frequency	Nivolumab (Flat Dose[a]) Dosing Frequency	NKTR-214 Dose (mg/kg)	No. Patients Examined for Safety	Positive Biomarker Data and/or Evidence of Clinical Activity?
NKTR-214 Monotherapy	q3w	n/a	0.003, 0.006, 0.009, 0.012	22	Yes
	q2w	n/a	0.006	6	Yes
NKTR-214+ Nivolumab	q3w	q2w	0.006	4	Yes
	q2w		0.006	3	Yes
	q3w		0.006	25	Yes
	q2w		0.003	3	Yes
	q3w		0.009	3	Yes

Abbreviations: q2w = every 2 weeks; q3w = every 3 weeks; n/a = not applicable.

a. Nivolumab q2w = 240 mg, q3w = 360 mg.

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The Safety Review Committee reviewed the totality of data and concluded the following for all 5 combination dose cohorts with a data cut of October 05, 2017:

- Two patients at the NKTR-214 0.009 mg/kg q3w + nivolumab 360 mg q3w dose level experienced dose limiting toxicities: Grade 3 hypotension and Grade 4 metabolic acidosis, each of which resolved within 5 days and the patients continued on treatment at a lower dose of NKTR-214.
- There were no Grade ≥ 3 treatment-related adverse events (TRAEs) at NKTR-214 0.006 mg/kg q3w + nivolumab 360 mg q3w: the recommended Phase 2 dose.
- TRAEs that occurred in ≥ 50% of the patients included fatigue, flu-like symptoms (combined MedDRA preferred terms of influenza-like illness, pyrexia, and chills), rash (combined MedDRA preferred terms of rash, rash erythematous, rash macular, rash maculopapular, and rash pruritic), and pruritus.
- TRAEs were consistent across all five dose cohorts.
- Management guidelines implemented in the combination program for hypotension were effective to mitigate the risk for Grade ≥ 3 hypotension.
- No Grade ≥ 3 immune-mediated AEs were observed.
- Cytokine-related AEs such as fever, chills, pruritus, fatigue, and rash are predictable based on the mechanism of action and were generally of mild severity and short duration.
- The addition of NKTR-214 did not exacerbate nivolumab-related AEs that are commonly classified as immune-mediated AEs.
- NKTR-214 alone or in combination with nivolumab did not produce capillary leak syndrome, which is commonly observed in patients treated with high-dose IL-2.

Tumor response data were available as of October 05, 2017 for 34 patients, including 10 with metastatic melanoma, 19 with renal cell carcinoma (RCC), and 5 with non-small cell lung cancer (NSCLC). Of these 34 response-evaluable patients, 24 were treated at 0.006 mg/kg NKTR-214 with nivolumab 360 mg flat dose q3w; 17 patients had partial or complete responses and 13 had stable disease. Given the totality of data, including safety/tolerability, reproducible PK, dose-independent PD profile, immune cell activation, and promising efficacy data (see Clinical Experience with NKTR-214 in Section 2.1.4), the Safety Review Committee approved NKTR-214 0.006 mg/kg q3w plus nivolumab 360 mg q3w as the recommended dose to be administered in the expansion cohorts included in Part 2 of the study.

Additional dosing schedules may be explored during the expansion phase. Any change to the recommended dose or frequency (either of NKTR-214 or nivolumab) will require endorsement by the Safety Review Committee, prior written approval by ethics committees, and notification to/approval by regulatory authorities in accordance with regulatory requirements. Where permitted this notification may be in the form of an administrative letter followed by a formal protocol amendment (see Section 11.1 on Changes to the Protocol).

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5.3.3.1 Update of Safety and Efficacy Data

As of February 8, 2018, a total of 130 patients have received NKTR-214 in combination with nivolumab for various tumor types in this study. Of the 130 patients, 38 were in the dose escalation part of the study and 92 in the dose expansion part. A total of 117 patients have received the RP2D (NKTR-214 0.006 mg/kg q3w with nivolumab 360 mg q3w) in the dose escalation phase (25 patients) and the dose expansion phase (92 patients).

The majority of treatment-emergent AEs (TEAEs) were mild in severity, and the most common treatment-related AEs were Grade 1 or 2 flu-like symptoms (in 70.8% of patients), Grade 1 or 2 fatigue (47.7%), and Grade 1 or 2 rash (42.3%). Overall, 14 patients (10.8%) experienced treatment-related AEs of Grade 3 or 4 severity, the most common being syncope in 3 patients (2.5%). No patient discontinued study treatment due to treatment-related AEs and there were no treatment-related deaths.

Two patients at the NKTR-214 0.009 mg/kg q3w + nivolumab 360 mg q3w dose level experienced dose limiting toxicities: Grade 3 hypotension and Grade 4 metabolic acidosis, each of which resolved within 5 days and the patients continued on treatment at a lower dose of NKTR-214.

Five patients in the dose escalation phase had a total of 7 SAEs that were considered possibly related or related to NKTR-214 or nivolumab, or both, and 9 patients in the dose expansion phase had a total of 12 SAEs that were considered possibly related or related to NKTR-214 or nivolumab, or both. The individual SAEs were as follows:

- related to NKTR-214 only: Grade 1 face edema, Grade 2 headache, Grade 2 and Grade 3 pyrexia (2 patients), Grade 3 lung infection (empyema), and Grade 3 rash erythematous
- related to nivolumab only: Grade 1 autoimmune hepatitis, Grade 2 hypophysitis, and Grade 2 hypothyroidism
- related to NKTR-214 and nivolumab: Grade 1 pyrexia, Grade 2 autoimmune hypothyroidism, Grade 3 hypotension, Grade 3 hyperthyroidism, Grade 3 syncope, Grade 3 rash, Grade 3 dehydration, Grade 3 pain, Grade 3 hyponatremia, and Grade 4 acidosis.

Tumor response data were available for the 25 patients who received the RP2D in the dose escalation phase, including 7 with metastatic melanoma, 11 with renal cell carcinoma (RCC), and 3 with non-small cell lung cancer (NSCLC) (Table 7). Of these 24 response-evaluable patients, 15 patients (62.5%) had partial or complete responses and 5 (20.8%) had stable disease.

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Table 7: 16-214-02: Overall Investigator-Assessed Tumor Response for Patients Treated at the NKTR-214 Recommended Phase 2 Dose and Nivolumab 360 mg q3w in the Dose Escalation Study Phase

	1L RCC - Esc (N=11)	2L RCC - Esc (N=4)	Melanoma - Esc (N=7)	NSCLC - Esc (N=3)	All (N=25)
Efficacy Evaluable Population[a] - RECIST 1.1, n (%)	11	3	7	3	24
ORR (CR+PR)	7 (63.6%)	0	6 (85.7%)	2 (66.7%)	15 (62.5%)
95% CI of ORR	30.8%, 89.1%	0%, 60.2%	42.1%, 99.6%	9.4%, 99.2%	40.6%, 81.2%
CR	0	0	1 (14.3%)	1 (33.3%)	2 (8.3%)
PR	7 (63.6%)	0	5 (71.4%)	1 (33.3%)	13 (54.2%)
SD	1 (9.1%)	3 (100.0%)	1 (14.3%)	0	5 (20.8%)
DCR (CR+PR+SD)	8 (72.7%)	3 (100.0%)	7 (100.0%)	2 (66.7%)	20 (83.3%)
PD	3 (27.3%)	0	0	1 (33.3%)	4 (16.7%)

CR = complete response; DCR = disease control rate; Esc =patient as part of dose escalation study phase; ND = not done. PD = progressive disease; PR = partial response; SD = stable disease; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors

a. Number of patients with baseline and at least one post-baseline tumor assessment.

Source: Tables 14.2.1.2 and 14.2.2.2; Database: 07Feb2018; Created: 12Mar2018

5.3.4 Part 2: Dose Expansion

All procedures are outlined in the Schedule of Events (Section 1.2). Enrollment into a dose expansion cohort will commence once the RP2D is established and communicated to sites. Approximately 925 patients will be enrolled with a range of 18-39 per indication, except for Cohort 3h in which target enrollment may be approximately 100 patients, depending on early efficacy results in the initial 20 evaluable patients (Table 8). During dose expansion, patients who drop out prior to completion of Cycle 1 will not be replaced. Sponsor may choose not to open or complete all expansion cohorts.

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Table 8: Part 2 Treatment Cohorts (All Patients Receive NKTR-214 plus Nivolumab[a])

Indication	Cohort	Description
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
RCC	2a[b]	1L
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Urothelial	4a[b]	1L, cisplatin ineligible
	4a[b,c]	1L, refused standard of care
	[redacted]	[redacted]
	[redacted]	[redacted]

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Table 8: Part 2 Treatment Cohorts (All Patients Receive NKTR-214 plus Nivolumab[a]) (Cont'd)

Indication	Cohort	Description
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: CRC = colorectal cancer; HR+ HER2- BC = hormone-receptor positive, HER2-negative breast cancer; I-O = immuno-oncology; MSI = microsatellite instability; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; RP2D = recommended Phase 2 dose; SCLC = small cell lung cancer; TNBC = triple-negative breast cancer

a. All patients receive the RP2D: NKTR-214 0.006 mg/kg q3w with nivolumab 360 mg q3w

b. Cohorts open for enrollment before Amendment 6.

c. For sites located in Italy only: patients may not be enrolled if they have 1L urothelial cancer with cisplatin-eligible disease.

5.3.4.1 Other Anti-Cancer Study Drugs Administered in Part 2

In Part 2, patients in the 4 cohorts described below have additional anti-cancer study drugs administered with the RP2D (NKTR-214 0.006 mg/kg q3w with nivolumab 360 mg q3w). The details of the dosing regimens for these cohorts are described below. For each of these 4 cohorts, an initial group of 6 patients should be enrolled and observed for at least 1 cycle before additional patients are enrolled into the cohort. The Safety Review Committee will review these patients before full enrollment will occur. Institutional guidelines for administration of other anti-cancer therapies should be followed.

5.3.4.1.1 Cohorts 3d.1 and 3d.2: NSCLC (1L nonsquamous)

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5.3.4.1.2 Cohort 3e: NSCLC (1L squamous)

[redacted]

5.3.4.1.3 Cohort 5b: TNBC in Combination with Nab-Paclitaxel

[redacted]

5.3.4.1.4 Cohort 5c: TNBC in Combination with Eribulin

[redacted].

5.3.5 Part 3: Schedule Finding for Triplet (NKTR-214, Nivolumab, and Ipilimumab)

[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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5.3.6 Part 4: Dose Expansion of Triplet (NKTR-214 plus Nivolumab plus Ipilimumab)

[redacted]

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[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
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	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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5.3.7 Monitoring, Vital Signs, and Hydration Guidelines

The study site must be equipped for medical emergencies.

5.3.7.1 Frequent Vital Signs

Refer to Section 7.14 for vital sign measurements.

For Part 1 Cycle 1 only, monitoring windows will be as follows:

- Cycle 1 Day 1 (dosing day) monitor predose, and every hour for 3 hours (q1h × 3)

- Cycle 1 Day 2 monitor every hour for 4 hours (q1h × 4)

Cycle 1 Day 3 monitor every hour for 2 hours (q1h × 2)

For Parts 2, 3, and 4, vital signs should be monitored according to the Appendix 2 Schedule of Assessments.

If the patient experienced a Grade ≥ 2 infusion-related reaction or hypotension on the dosing day, the patient may be monitored overnight at the discretion of the Investigator. Longer periods of monitoring may be implemented at the discretion of the Investigator.

5.3.7.2 Hydration Guidelines

Important safety information and hydration instructions are to be provided to patients.

For Cycle 1, administer at least 1 liter of IV fluid on Days 1 and 2. During Cycle 2 and beyond, administer at least 1 liter of IV fluid on Day 1. For all cycles, recommend at least 2 liters per day of self-administered oral hydration on Days 2 to 5. If deemed necessary by the Investigator, administration of IV fluid may be given on Day 2. Advise patients to restrain from strenuous activity and avoid long hot showers and saunas for Days 1 to 5 of every cycle. Per clinical judgment, IV fluids may be administered in any cycle. The Investigator may decide to forego administering IV fluids to a patient if this is deemed in the best interest of the patient (e.g., evidence of fluid overload).

5.3.7.3 Optional Home Health Visits

In addition to planned study site visits, vital signs (temperature, pulse, respiration, systolic and diastolic blood pressure, and oxygen saturation), concomitant medications, and potential AEs may be assessed at a Home Health visit as needed. The results of these measurements will be provided to the Investigator or designee. The Investigator will be responsible for assessing any AEs and for following up with the patient.

5.3.8 Duration of Treatment

Patients will be treated until:

- Disease progression
- Death
- Unacceptable toxicity
- Symptomatic deterioration
- Achievement of maximal response or up to 2 years of therapy
- Investigator's decision to discontinue treatment
- Patient decision to discontinue treatment

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- Patient withdraws consent
- Lost to follow up
- Nektar Therapeutics decides to terminate the study

5.3.9 Treatment Beyond Progression

Accumulating evidence indicates that a minority of patients with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Patients will be permitted to continue on treatment beyond initial RECIST 1.1-defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and without rapid disease progression.
- Continue to meet all other study protocol eligibility criteria.
- Patient tolerates study drug(s).
- Patient has stable ECOG performance status of 0 or 1.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., central nervous system metastases).

The assessment of clinical benefit should take into account whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the Medical Monitor, and an assessment of the risk/benefit of continuing with study drug(s) must be documented in the study records. The ICF contains language explaining treatment beyond progression; should the Investigator recommend continuing treatment following disease progression, the patient must be re-consented prior to continuing study treatment.

For patients who stay on treatment beyond RECIST 1.1-defined PD, all study procedures (Section 1.2) should be performed continuously, including radiographic assessment by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI) every 8 weeks as described in Section 8.2. Patients will be discontinued from the treatment upon further evidence of disease progression, defined as an additional 20% or greater increase in the total tumor burden from the time of initial disease progression, unless otherwise approved by the Medical Monitor. The total tumor burden is calculated as the sum of the longest diameter (SLD) of all target tumors and SLD of all new measurable lesions. A new lesion is measurable if the longest diameter is at least 10 mm except for pathological lymph nodes, which must have a short axis of at least 15 mm. Any new lesions that are non-measurable at the time of initial appearance and become measurable later will be included in the calculation of total tumor burden.

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5.4 End of Treatment (EOT)

Patients may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment. Patients may discontinue treatment of all or one of the study drugs based on AEs (see Section 5.13 pertaining to Study Drug Discontinuation). The EOT visit should occur 30 (+10) days after study therapy is permanently discontinued or before a new antineoplastic regimen starts.

Reasons for EOT are listed below:

- Disease progression in the absence of clinical benefit as determined by the Investigator.
- Occurrence of a clinically significant AE found to be unacceptable or non-resolution of a clinically significant AE for > 6 weeks.
- Symptomatic deterioration in the absence of tumor progression per RECIST 1.1.
- Achievement of maximal response after at least 6 months of dosing with study drug(s); patients may receive a maximum of 2 years therapy under this protocol.
- Noncompliance of the patient with protocol-mandated procedures based on the judgment and agreement of both the Investigator and Sponsor.
- At the discretion of the Investigator (continued participation is no longer in the patient's best interest in the opinion of the Investigator).
- If a female patient becomes pregnant, administration of the study drugs must be discontinued immediately.
- Patient's decision to discontinue treatment
- Patient withdraws consent for the study.
- Lost to follow-up (defined as after three attempts at contact by phone followed by one attempt by sending a certified letter).
- The study is terminated by the Sponsor.

In the event of a patient's withdrawal, the Investigator will promptly notify the Sponsor and make every effort to complete the End of Treatment procedures specified in the Schedule of Events (Section 1.2).

A patient may also be withdrawn from investigational product/study by the Sponsor, Regulatory Authorities, or Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs).

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5.5 Long-Term Follow-up

Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. Timing for long-term follow-up will be as follows:

- Upon discontinuation of immune checkpoint inhibitor therapy (nivolumab and/or ipilimumab), the long-term follow-up visits should occur every 30 (+ 10) days for 3 visits after the last dose of immune checkpoint inhibitor. Thereafter, the long-term follow-up should occur every 90 (±10) days for survival status (this may be captured by phone).
- Per clinical judgment, the patient may come in earlier.
- All patients will be contacted for survival every 3 months.
- For patients who do not discontinue study drug treatment for progression of disease by RECIST v 1.1 or withdrawal of consent, radiographic tumor assessments will occur every 90 (+ 10) days and continue to be collected until disease progression, patient withdraws consent, death, initiation of a new systemic antineoplastic regimen, or study termination by the Sponsor.
- In cases of a positive immunogenicity test result for NKTR-214, see Section 5.9.

For AE and SAE reporting periods, please refer to Sections 7.5 and 7.7.

5.6 End of Study

End of study is defined as no more than 3 years after the last patient received their first dose of NKTR-214 or Sponsor decision to terminate the study, whichever comes first. Survival data may be collected beyond end of study.

5.7 Tumor and Radiographic Assessments

Tumor assessments for all patients will be performed at Screening and every 8 weeks (± 7 days). If a patient has an unconfirmed PR or CR, an early scan is recommended 4 weeks later (e.g., if the initial observation of PR was seen at Week 8, a Week 12 scan should occur); subsequent tumor assessments must remain on the original 8-week assessment schedule (i.e., at Week 16, Week 24, then at Week 32, Week 40, etc.) For patients with unconfirmed progressive disease, subsequent tumor assessments must remain on the original 8-week assessment schedule (i.e., at Week 16, Week 24, then at Week 32, etc.), unless an early scan is clinically indicated. Tumor response will be evaluated using RECIST 1.1 as the primary and irRECIST as an exploratory measure (Section 8.0).

Radiographic assessments (chest/abdomen/pelvis) are required for all patients for tumor measurements. Imaging of the brain on-study at 8-week intervals must occur for patients with known brain metastases at baseline.

Documented tumor measurements are required using CT scans, MRI, physical examination, and/or digital photography, as appropriate. Any imaging used to assess disease at any time point will be submitted for an independent radiology review.

The same method of assessment (CT or MRI and/or digital photography) and the same technique for acquisition of images must be used for all study assessments (contrast must be used unless medically contraindicated). Baseline imaging should be done at the same institution/facility that will be used to measure response during the patient's participation in the study. Radiographic assessments and efficacy analyses will be conducted by the Investigator site as well as the independent radiology review.

5.8 Pharmacokinetic Measurements

Blood samples for pharmacokinetic (PK) analyses of NKTR-214 and its metabolites will be collected in all cycles.

> Part 1: For Cycle 1 only, blood samples will be collected on Days 1 to 5, 8, and 11. PK sample times are predose and at the following times after initiation of NKTR-214 dosing: 30 min ± 2 min (end of NKTR-214 infusion), 1.5 hr ± 10 min, 3 hr ± 10 min, and 6 hr + 2 hrs. PK assessments for Cycles ≥ 2 will be on Day 1 (predose and 30 min ± 2 min [end of NKTR-214 infusion]) and Day 8.
>
> For all other Parts of the study except Part 1, blood samples will be collected according to the Appendix 2 Schedule of Assessments.

Blood samples for PK analyses of nivolumab and ipilimumab will be collected as follows:

> Part 1: predose Cycle 1 Day 1, end of infusion Cycle 1 Day 1, and predose Cycle 3 Day 1, Cycle 8 Day 1, Cycle 16 Day 1, Cycle 24 Day 1, Cycle 36 Day 1 or a maximum of 2 years
>
> For all other Parts of the study except Part 1, blood samples will be collected according to the Appendix 2 Schedule of Assessments.

In the event of a possible study drug(s)-related serious adverse event (SAE) throughout the study, additional PK blood samples may be drawn as close to the event as possible to help characterize any possible relationships between drug exposure and the clinical event.

Blood samples for PK analysis will be collected and processed as outlined in a Laboratory Manual that will be provided to the site. All on-treatment time points are intended to align with days on which study drug is administered; if dosing occurs on a different day, the PK sampling should be adjusted accordingly. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

For all PK blood samples, the date and actual time collected must be recorded.

5.9 Immunogenicity Measurements

Immunogenicity samples for NKTR-214 will be drawn as follows:

> Part 1: predose Cycle 1 Day 1, predose on Cycle 2 Day 1 and predose on Day 1 of all odd-numbered cycles thereafter (Cycles 3, 5, 7, etc.), follow-up visits, and EOT.
>
> For all other Parts of the study except Part 1, according to the Appendix 2 Schedule of Assessments.

If the EOT sample tested positive for immunogenicity, additional samples may have to be drawn at subsequent follow-up visits.

Immunogenicity samples for nivolumab in Part 1 will be collected as follows: predose Cycle 1 Day 1, and predose Cycle 3 Day 1, Cycle 8 Day 1, Cycle 16 Day 1, Cycle 24 Day 1, Cycle 36 Day 1, or a maximum of 2 years. If dosing occurs on a different day, the immunogenicity sampling should be adjusted accordingly.

Immunogenicity samples for nivolumab in Part 2 and immunogenicity samples for nivolumab and ipilimumab in Parts 3 and 4 will be collected according to the Appendix 2 Schedule of Assessments. If dosing occurs on a different day, the immunogenicity sampling should be adjusted accordingly.

In addition, for Cycle 1 only, one serum sample to assess for complement activation will be collected within 30 minutes of the end of the NKTR-214 infusion and before the start of nivolumab.

Serum samples will be collected and processed as outlined in the Laboratory Manual that will be provided to the site.

5.10 Biomarker Measurements (Blood and Tumor Collection)

Blood and tumor tissue biopsies will be collected and processed as outlined in the Laboratory Manual that will be provided to the site. Refer to the Laboratory Manual for specific instructions on sample processing, storage, and shipping.

5.10.1 Blood Biomarker Collection Times and Analysis

For Parts 1 through 4, a blood biomarker sample should be drawn prior to dose on Day 1, and on Day 8 according to the Appendix 2 Schedule of Assessments. If sufficient data are collected, the Sponsor may notify sites in writing to stop post-treatment blood collection on Day 8 of Cycles 3+. If the optional tumor biopsies at least 30 days after Cycle 1 Day 1 but prior to the Week 8 scan and at suspected or known disease progression are collected, collect an additional biomarker blood sample at the same time. Based on ongoing biomarker analysis, samples may be taken at

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different time points or stopped. The whole blood or peripheral blood mononuclear cells isolated from whole blood correlative pharmacodynamic samples will be analyzed by flow cytometry for changes in markers of immune cell populations, including, but not limited to, markers for T lymphocytes, B lymphocytes, natural killer cells, monocytes, memory T cell subsets, Tregs, and T cell activation. In addition, whole blood samples will be used for evaluation in assays of immune function such as stimulated cell activation (assessed by marker expression, cytokine secretion, proliferation, etc.), microRNA/messenger RNA analysis, and genetic profiling, including germline mutation testing, and circulating tumor deoxyribonucleic acid (DNA).

All remaining samples at the end of the study will be deidentified and moved into long-term storage for up to 15 years for future analysis, after which time the samples will be destroyed.

5.10.2 Tumor Tissue Biopsy Collection Times and Analysis

A fresh tumor biopsy obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen (fine-needle aspiration, cytology specimens, and bone lesions are not acceptable) will be required during Screening. Sufficient, recent tumor tissue obtained within 6 months prior to enrollment from a metastatic tumor lesion or from an unresectable primary tumor lesion which has not been previously irradiated (formalin-fixed paraffin-embedded block or minimum of 20 slides, obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen) may be submitted in lieu of a fresh tumor biopsy during the Screening period. Exceptions may be made with the Sponsor's Medical Monitor approval in cases where fresh tumor tissue and/or archival tumor samples are inaccessible.

Target lesions should not be biopsied unless there are no other lesions suitable for biopsy. If a target lesion is used for biopsy, the lesion must be ≥ 2 cm in the longest diameter.

One on-treatment tumor biopsy will be collected during Days 15-21 in Cycle 1; 1 optional on-treatment tumor tissue biopsy may be collected at least 30 days after Cycle 1 Day 1 but prior to the Week 8 scan. An additional tumor tissue biopsy may be collected at the time of suspected or known disease progression. In Parts 2 and 4 only, on-treatment tumor biopsies will be performed for a minimum of 10 patients per tumor indication.

Pretreatment and on-treatment biopsies should be taken from the same lesion, if feasible. Biopsies should be performed on lesions that have not been exposed to prior radiation. Tumor tissue biopsies will be used for characterization of infiltrating immune cell populations using a panel of markers, using IHC, flow cytometry, mass spectroscopy, or other similar techniques. Biopsy samples may also be used to investigate molecular signatures. DNA and/or RNA may be extracted from these samples for somatic mutation analysis and gene expression analysis. Genes to be assayed may include, but not be limited to, those with known driver mutations in solid tumors. These samples will be analyzed by the Sponsor or designee.

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5.10.3 Stool Sample Analysis

A stool sample from a single bowel movement will be collected by patients participating in Parts 2-4 of the study prior to administration of the first dose and at Cycle 3 Day 1 ± 10 days. Patients will be provided with a materials kit and instructions for collecting the stool sample. Stool samples will be processed to extract and sequence microbial DNA and RNA as outlined in a Laboratory Manual.

5.11 Determination of Dose-Limiting Toxicities (DLTs)

Based on the nonclinical toxicology, safety data from the dose escalation study (Study 15-214-01; NCT02869295) and the half-lives of NKTR-214 and metabolites (approximately 20 hours), drug-related toxicity is most likely to occur 1 to 5 days following treatment. In Part 1 of the study, DLTs will be assessed during the DLT window shown in Table 5. If DLTs are not observed, dose escalation will be permitted and enrollment of the next dosing cohort may begin. Intra-patient dose escalation is not permitted. In Part 3, the DLT evaluation period will begin with the first dose of ipilimumab and the evaluation period will be a minimum of 3 weeks (21 days). If DLTs are not observed, patients will continue to enroll until 12 patients have been evaluable for safety. Grading of AEs is described in Section 7.3.

5.11.1 DLTs Related to Study Drug(s)

Examples of AEs related to study drug(s) that will be defined as a DLT include the following:

- Any Grade ≥ 3 drug-related non-hematological AE that does not resolved to Grade 1 or baseline within 7 days except those listed in Section 5.11.2.
- Any drug-related Grade ≥ 2 myocarditis, Grade ≥ 2 uveitis, Grade ≥ 3 pneumonitis, or Grade ≥ 3 neurotoxicity
- Any Grade 4 drug-related hematological AE that is clinically significant.
- Any Grade 4 nausea or vomiting.
- Any Grade ≥3 drug-related hypotension lasting > 48 hours post-dose, cytokine-release syndrome, capillary leak syndrome, pulmonary edema, symptomatic hypereosinophilic syndrome, or qualifying drug-induced liver injury (DILI)

All AEs that meet DLT criteria must be recorded in the electronic data capture system within approximately 24 hours of awareness.

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5.11.2 Grade 3 or 4 AEs that Should Not be Considered a DLT

The following Grade 3 or 4 AEs should not be considered a DLT:

- Endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyper- or hypothyroidism, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose intolerance managed with glucose-controlling agents.
- Asymptomatic amylase or lipase elevations.
- Lymphopenia < 14 days in duration or not associated with clinical manifestations.
- Electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Grade 3 nausea or vomiting that can be medically managed to ≤ Grade 2 within 72 hours.
- Grade 3 hypotension during Cycles 1 or 2 that lasts ≤ 48 hours post-dose.
- Fatigue that improves to ≤ Grade 2 within 7 days.

5.12 Delayed Dose-Limiting Toxicities (DLTs)

Delayed DLTs are AEs as defined in Section 5.11.1 that occur after the DLT window listed in Table 5. Delayed DLTs will not be used to determine the MTD for dose escalation. Delayed DLTs will be collected and evaluated by the Investigators and the Medical Monitor on an ongoing basis.

All AEs that meet DLT criteria must be recorded in the electronic data capture (EDC) system within 24 hours of awareness.

5.13 Dose Delay and Reduction Criteria

Dose delays of more than 1 drug are allowed for management of treatment-related toxicities during a give treatment cycle. For dose delay and reduction criteria, see grading of AEs described in Section 7.3. Tumor assessments for all patients should continue as per protocol even if dosing is delayed.

5.13.1 Nivolumab Dose Delay Criteria

Dose reductions for nivolumab are not permitted in this study. Nivolumab may be delayed based on observed drug-related toxicities. If nivolumab is delayed, NKTR-214 or ipilimumab administration can continue in the absence of NKTR-214- or ipilimumab-related toxicity that would warrant a dose delay. If the Investigator cannot determine which study drug is causing the toxicity, then all study drugs should be delayed.

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Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 pneumonitis (in the case of Grade 1 pneumonitis, delay should be considered but is not required).
- Any Grade ≥ 2 non-skin, drug-related AE, except for fatigue and asymptomatic laboratory abnormalities that are corrected with supplementation/appropriate management within 72 hours of onset, or Grade 3/4 endocrinopathies that can be successfully treated with administration of replacement therapy.
- Any Grade ≥ 3 skin drug-related AE, except when occurring during the first 48 hours of NKTR-214 administration.
- Any Grade 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, creatinine, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require a dose delay.
  - If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
  - Grade 2 serum creatinine requires a dose delay, if not resolved to a Grade 1 or baseline prior to the next dose.
  - Any Grade 3 or Grade 4 drug-related amylase and/or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.
- Any AE, laboratory abnormality, or inter-current illness that, in the judgment of the Investigator, warrants delaying the dose of study medication.

5.13.2 Ipilimumab Dose Delay Criteria

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5.13.3 NKTR-214 Dose Delay and Reduction Criteria

Dose delays and reductions are permitted for NKTR-214. Per recommendation of the Investigator and approval of the Sponsor's Medical Monitor, NKTR-214 may be delayed or reduced (to 0.003 mg/kg) based on observed drug-related toxicities. If NKTR-214 is delayed, nivolumab or ipilimumab administration can continue in the absence of nivolumab- or ipilimumab-related toxicity that would warrant a dose delay.

NKTR-214 may be delayed or reduced for the following reasons:

- Grade 1 or 2 toxicity: No requirement for dose delay or dose reduction. If the toxicity persists at Grade 2 following completion of Cycle 1, a dose delay (of either NKTR-214, nivolumab and/or ipilimumab) or dose reduction (of NKTR-214) may be implemented at the discretion of the Investigator with the approval of the Medical Monitor.

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- Grade 3 or higher toxicity: NKTR-214 may be withheld if toxicity cannot be managed by adequate medical intervention. NKTR-214 dosing may resume at the same NKTR-214 dose or at a lower NKTR-214 dose level when toxicity resolves to Grade 1 or returns to baseline, except for instances where the potential recurrence of the event poses an undue risk for the patient.

5.13.4 Cohorts 3d.1 and 3d.2 (NSCLC) Dose Delay and Reduction Criteria for Platinum and Pemetrexed

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5.13.5 Cohort 3e (NSCLC) Dose Delay and Reduction Criteria for Platinum and Taxane

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Table 17: Recommended Dose Modifications for Non-Hematologic Toxicity Platinum and Taxane

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5.13.6 Nab-Paclitaxel Dose Delay and Reduction Criteria

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5.13.7 Eribulin Dose Delay and Reduction Criteria

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5.13.8 Criteria to Resume NKTR-214, Nivolumab, or Anti-Cancer Study Drugs

Patients will be permitted to resume study drug(s) at the same dose level(s) following resolution of an AE to Grade ≤ 1 or to baseline within 6 weeks after the last dose, with the exception of patients who meet criteria for permanent discontinuation as specified in Section 5.13.9. Patients who meet criteria for permanent discontinuation must not receive further study therapy.

If the decision is made to resume study drug(s) dosing, the patient should restart treatment on the next regularly scheduled study drug(s) dosing visit. Skipped doses are not to be replaced.

Patients may resume treatment when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT **or** total bilirubin.
- Patients with combined Grade 2 AST/ALT **and** total bilirubin values meeting discontinuation parameters (see Section 5.13.9) should have treatment permanently discontinued.

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- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible to resume study drug(s) treatment if discussed with and approved by the Medical Monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor.
- Patients who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3.

Dose delay of NKTR-214 that results in treatment delay of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 5.13.9. However, if the toxicity resolves to ≤ Grade 1 or baseline > 6 weeks after the last dose, but the patient does not otherwise meet the criteria for permanent discontinuation (see Section 5.13.9), and the Investigator believes that the patient is deriving clinical benefit, then the patient may be eligible to resume the study drug(s) following the approval of the Medical Monitor.

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5.13.9 Permanent Treatment Discontinuation Criteria

Patients meeting any of the following criteria will be required to permanently discontinue all assigned study drug(s). However, with Medical Monitor approval, NKTR-214 treatment may continue if the toxicities listed below are considered related to nivolumab and/or ipilimumab and/or other anti-cancer study drugs only.

- Disease progression in the absence of clinical benefit (see details regarding continuing treatment beyond initial assessment of progression per RECIST 1.1 in Section 5.3.9).
- Clinical deterioration, as assessed by the Investigator.
- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 6 weeks **or** requires systemic treatment.
- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve following dose delay and systemic steroids (also see Pulmonary Adverse Event Management Algorithm in the nivolumab Investigator's Brochure).

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- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for uveitis, pneumonitis, myocarditis, bronchospasm, diarrhea, colitis (ipilimumab and nivolumab must be discontinued for ≥ Grade 3 colitis related to ipilimumab), neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
  - Grade 3 drug-related uveitis, pneumonitis, myocarditis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction **of any duration** requires discontinuation.
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with clinically significant bleeding requires discontinuation.
    - Any drug-related liver function test abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm in the nivolumab Investigator's Brochure):
      - AST or ALT > 5 × to 10 × ULN for > 2 weeks
      - AST or ALT > 10 × ULN
      - Total bilirubin > 5 × ULN
      - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia ≤ 14 days in duration
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

  - Grade 4 drug-related endocrinopathy AEs such as adrenal insufficiency, adrenocorticotropic hormone deficiency, hyper- or hypothyroidism, or glucose intolerance, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids at ≤ 10 mg of prednisone or equivalent per day, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor.

- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued treatment.
- Any dosing delay lasting > 6 weeks after the last dose, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a patient with a dosing delay lasting > 6 weeks after the last dose and with no more than 3 missed doses, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
  - Dosing delays > 6 weeks after the last dose that occur for nondrug-related reasons, may be allowed if approved by the Medical Monitor. Prior to re-initiating treatment in a patient with a dosing delay lasting > 6 weeks after the last dose and with no more than 3 missed doses, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed, and patients must otherwise meet the criteria for continued treatment at the time re-initiation of study therapy is considered.

5.14 Management Algorithms for Immune-mediated AEs Associated with Immuno-Oncology Agents

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms including the use of systemic corticosteroids (see the nivolumab and ipilimumab Investigator's Brochures) have been developed to assist Investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

- Other immune-mediated AEs (as defined in the nivolumab and ipilimumab Investigator's Brochures)

5.15 Treatment of NKTR-214, Nivolumab, or Ipilimumab-Related Infusion Reactions

Infusion reactions have been infrequently reported during infusions with NKTR-214, nivolumab, or ipilimumab. If such a reaction were to occur with either the NKTR-214, nivolumab, or ipilimumab infusion, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions regardless of seriousness should be reported within 24 hours to the study Medical Monitor and Nektar Drug Safety (See Section 7.10). Infusion reactions should be graded as described in Section 7.3.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For **Grade 1** symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at the bedside and monitor the patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before subsequent infusions.

For **Grade 2** symptoms (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the NKTR-214, nivolumab, or ipilimumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at the bedside and monitor the patient until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. If symptoms recur after restarting the nivolumab or ipilimumab infusion, then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, remain at the bedside, and monitor the patient until resolution of symptoms.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before the infusion. If necessary, corticosteroids (up to 25 mg of Solu-Cortef or equivalent) may be used.

For **Grade 3 or Grade 4** symptoms (severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of NKTR-214, nivolumab, or ipilimumab. Begin an IV infusion of normal saline and treat the patient as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Nivolumab or ipilimumab will be permanently discontinued. The patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at the bedside and monitor the patient until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

5.16 Prior and Concomitant Medications

Complications, including fatal events, have occurred in patients who received allogeneic hematopoietic stem cell transplantation (HSCT) before or after nivolumab.

Premedications should not be administered prior to the initial administration of NKTR-214, nivolumab, or ipilimumab, but if a patient reports symptoms (such as nausea and/or vomiting), prophylactic use of anti-emetics may be used.

Recording of prior medications should include prior cancer treatments: previous immunotherapy, chemotherapy, targeted therapy, radiation, over-the-counter (OTC) medications, herbs, and dietary supplements.

All medications (prescription and OTC), vitamin and mineral supplements, and/or herbs taken by the patient from Screening through the EOT visit will be documented and recorded, including start and stop date, dose and route of administration, frequency, and indication. Medications taken for a procedure (e.g., biopsy) should also be included.

5.17 Permitted Concomitant Medications

Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Patients with pre-existing adrenal impairment requiring corticosteroid supplementation may be at increased risk for hypotensive episodes during treatment with NKTR-214. For these subjects, their existing corticosteroid dose may be increased by an additional supplementation of up to 5 mg/day of prednisone, or

equivalent, for the first 4 days after administration of NKTR-214 based on an assessment of the degree of adrenal impairment and the extent of existing corticosteroid supplementation. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Use of corticosteroids for the management of autoimmune conditions (as outlined in the Investigator's Brochures for nivolumab and ipilimumab) is permitted.

Prophylaxis for flu-like symptoms with either acetaminophen or ibuprofen is permitted on study per the Investigator's discretion. Prophylaxis for flu-like symptoms can be initiated on either Day 1 or Day 2 of the dosing cycle and may continue through Day 5 or longer as needed.

Prophylaxis for rash and/or pruritus with anti-histamines is permitted on study per the Investigator's discretion. Prophylaxis for rash and/or pruritus can be initiated on either Day 1 or Day 2 of the dosing cycle and may continue through Day 5 or longer as needed.

Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed. Prior palliative radiotherapy must have been completed > 14 days before administration of first dose of study drug. On-study palliative radiotherapy may occur after discussion with the Medical Monitor; on-study radiotherapy to target lesions is not permitted.

5.18 Prohibited Concomitant Medications

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.17), defined as a daily dose of greater than 10 mg prednisone
- Any antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or investigational agent) is prohibited during the study. Radiation therapy may be permitted following a discussion with the Medical Monitor.

Consideration should be given to discontinuing antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (e.g., alpha blockers for benign prostatic hypertrophy) prior to each dose of NKTR-214, particularly when therapy involves multiple anti-hypertensive drugs and classes other than thiazide diuretics. If discontinuing antihypertensive medications, discontinue no less than 12 hours and no more than 48 hours prior to each dose of NKTR-214. Antihypertensive medications may be reinstituted in between doses of NKTR-214 if the diastolic pressure exceeds 90 mm Hg and/or the systolic pressure exceeds 160 mm Hg.

In addition, prohibited medications listed in the current nivolumab or ipilimumab prescribing information are not allowed. For cohorts that administer NKTR-214 and nivolumab in combination with cytotoxic chemotherapy, sites should follow prescribing guidelines listed in the current Package Insert or Summary of Product Characteristics.

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5.19 Adverse Events

All AEs, either reported by the patient or observed by study staff, will be recorded until the EOT visit (Section 5.4) or until a new antineoplastic regimen has been initiated. This trial will use the Medical Dictionary for Regulatory Activities (MedDRA) for coding all AEs. AEs will be summarized by preferred term, system organ class, grade of severity, and relationship to each study drug (NKTR-214 and/or nivolumab and/or ipilimumab).

5.20 Assigning Patient Numbers

Each patient will be assigned a unique patient number after signing the ICF. Patient numbers will be used on all patients' study information. Patient numbers will not be reassigned.

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6.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

6.1 NKTR-214 Drug Description and Formulation

The investigational drug product, NKTR-214, is formulated as a sterile lyophilized powder for reconstitution in single-use glass vials. Lyophilized NKTR-214 drug product will be reconstituted with sterile water for injection (SWFI), and diluted with commercially available Dextrose 5% in water for injection (D5W) or 0.9% NaCl solution (0.9% SSI). Each 5 mL, clear glass, single-use vial contains 1.1 mg of recombinant human interleukin 2 (rhIL-2) equivalents (including 0.1 mg of overage). NKTR-214 is formulated in 10 mM citrate buffer, 7% (w/v) trehalose, pH 4.0. Refer to the Pharmacy Manual for additional information.

6.2 NKTR-214 Drug Packaging and Labeling

NKTR-214 will be packaged and labeled according to current good manufacturing practices. Each vial will be labeled with the study drug number/name, strength, name of the Sponsor, storage condition, lot number, and the required cautionary statement.

6.3 NKTR-214 Drug Reconstitution and Handling

The instructions for reconstitution and administration of NKTR-214 drug product are described in the Pharmacy Manual.

6.4 NKTR-214 Drug Storage

NKTR-214 drug product should be stored in a secure, locked area with temperature at monitored -20°C (± 5°C), as specified on the drug label.

6.5 NKTR-214 Drug Shipment

Supply of NKTR-214 drug product will be shipped frozen (-20°C [± 5°C]) to the site pharmacy upon completion of the site activation process.

Please refer to the Pharmacy Manual for additional details for ordering drug supply.

6.6 Nivolumab, Ipilimumab, and Other Anti-Cancer Study Drugs Formulation, Reconstitution, Storage, and Packaging

Please refer to the Pharmacy Manual for details.

6.7 Study Drug Accountability and Reconciliation

NKTR-214, nivolumab, and ipilimumab will be supplied to the Investigator by Nektar Therapeutics or its designee. At selected sites, commercially available nivolumab may be locally procured with Sponsor approval. For other anti-cancer study drugs, commercially available supplies should be locally procured. Please refer to the Pharmacy Manual for details.

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Study drug supplies must be kept in an appropriate, secure, locked area and stored in accordance with the conditions specified on the labels.

The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to Nektar Therapeutics at the end of the study.

The Drug Accountability Log may record specifics to study drug dispensation such as:

- Records of product delivery, inventory, temperature monitoring, destruction, and return as per Sponsor's instructions.
- Doses prepared, time prepared, doses dispensed.
- Doses and/or vials destroyed.

The Drug Accountability Log will be reviewed by the monitor during site visits and at the completion of the study.

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7.0 ASSESSMENT OF SAFETY OR AEs AND SERIOUS AEs

7.1 AE Definition and Assessment

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, at any dose, not necessarily related to the treatment.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can also arise from any use of the drug and from any route of administration, formulation, dose, or overdose. This definition includes intercurrent illnesses or injuries, and exacerbation of preexisting conditions. Clinical laboratory, vital sign, or physical examination abnormalities will only be reported as AEs if they are deemed clinically significant by the Investigator (e.g., associated with signs and symptoms, require treatment, or require follow-up).

An AE does not include:

- A medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion); an AE is the underlying condition that leads to the procedure.
- Pre-existing diseases or conditions present or detected before start of study drug(s) administration that do not worsen or increase in severity or frequency after the administration of study drug(s).
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery for a condition that has not worsened on study, social and/or convenience admissions to grant families a respite in caring for a patient).
- Overdose of either study drug(s) or concomitant medication without any signs or symptoms.

7.2 Monitoring AEs

All AEs will be assessed by the Investigator and recorded, including, but not limited to, the following: the event term, the date of onset and resolution, seriousness, severity, relationship to study drug(s), outcome, treatment of the event, and action taken with the study drug(s). AEs will be reported starting immediately after the patient has been administered the first dose of study drug(s) until 30 (+ 10) days following the last study drug administered (Section 5.4) or until a new antineoplastic regimen has been initiated, whichever is first.

An event occurring after the patient has provided informed consent, but before the first dose of study treatment, will be collected as medical history unless the event is either new and attributed to protocol-mandated procedures by the Investigator or there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Under the latter 2 circumstances, the event will be considered an AE and will be captured as such.

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Example 1:

Thrombophlebitis associated with a blood draw for assessments required prior to dosing per protocol is an event that is related to protocol-mandated procedures. In this scenario, the event of "thrombophlebitis" will be captured as an AE, and it will be documented as being "unrelated" to study drug(s), as applicable.

Example 2:

An ankle sprain following an unexpected fall from a flight of stairs while at home, after the patient has provided informed consent, but before the first dose of study drug(s), is clearly unrelated to any protocol-mandated procedures and would therefore be captured as medical history.

7.3 Grading of AEs

The severity of an event and the seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of event is based on the patient/event outcome or action criteria. All AEs will be assessed for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 guidelines. If a particular AE is not listed in the NCI-CTCAE, the following criteria will be used:

- Grade 1 = Mild (event results in mild or transient discomfort, not requiring or needing only minimal intervention or treatment; does not limit or interfere with daily activities [e.g., insomnia, mild headache]).
- Grade 2 = Moderate (event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment [e.g., fever requiring antipyretic medication]).
- Grade 3 = Severe (event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention).
- Grade 4 = Life threatening or disabling.
- Grade 5 = Death.

AEs will be reported with an individual start and stop date for each level of severity.

7.4 Causality Relationship of AEs

The relationship of each AE to each study drug (NKTR-214 and/or nivolumab and/or ipilimumab and/or other cytotoxic chemotherapy) as applicable will be evaluated by the Investigator using the following definitions:

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- Not related: The AE is clearly not related to the study drug(s). The AE can be explained to be likely related to other factors such as concomitant medications or the patient's clinical state.
- Possibly related: The AE may be related to the investigational agent(s). A plausible temporal sequence exists between the time of administration of the investigational product and the development of the AE, and it follows a known response pattern to the investigational product. The reaction may have been produced by the patient's clinical state or other concomitant therapies or interventions.
- Related: The AE is clearly related to the investigational agent(s). A plausible temporal sequence exists between the time of administration of the investigational product and the development of the AE, and it follows a known response pattern to the investigational product. The occurrence of this AE can be confirmed with a positive re-challenge test or supporting laboratory data.

The causality criteria of related and possibly related will be considered "related" to the study drug(s) for regulatory reporting requirements.

7.5 AE Reporting and Follow-up

After initiation of study drug treatment, all AEs except for SAEs (Section 7.7) will be reported from the time of first study drug(s) administration until 30 (+ 10) days following the last study drug administered (Section 5.4) or until a new antineoplastic regimen has been initiated, whichever is first. All ongoing AEs will be followed until resolution, the patient is lost to follow-up, patient death, or until the EOT visit, whichever is earlier. In case the AE has not completely resolved by the EOT visit, the final outcome of these ongoing AEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable. Any new AEs occurring after the EOT visit will not be captured unless related to a study drug.

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. After initiation of study treatment, all SAEs will be reported until 100 days after discontinuation of dosing with nivolumab or ipilimumab if nivolumab or ipilimumab is the last study drug administered or 30 days after discontinuation with NKTR-214 or chemotherapeutic agents if NKTR-214 or a chemotherapeutic agent is the last study drug administered. After the end of the reporting period for SAEs, the investigator must report any SAE that is believed to be related to prior exposure to study treatment or protocol-specified procedure.

For specific instructions on identifying and reporting SAEs, see Sections 7.6 and 7.7.

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7.6 Serious AE Definition

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening, i.e., in the opinion of the Investigator, the AE places the patient at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization that occurs during the course of a patient's participation in a clinical study, except for those due to the following:
  - A surgery or procedure that was planned before the patient entered the study and which is part of the planned study procedure.
  - Nonmedical reasons, in the absence of an AE.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed above.

Death is an outcome of an AE and not an AE in itself. All events leading to death, regardless of causality, must be reported. An efficacy failure is not considered an SAE. "Life-threatening" means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity. "Inpatient hospitalization" means the patient has been admitted to a hospital for medical reasons for any length of time. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

7.7 Serious AE Reporting

Serious AEs occurring after the patient has provided informed consent, but before the first dose of study treatment, will be collected as medical history unless the event is either new and attributed to protocol-mandated procedures by the Investigator or there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Any new or clinically significant changes in the patient's medical and/or cancer history that occur immediately after the first dose of drug will be recorded as SAEs. All SAEs, believed to be related to study drug(s), with an onset within 100 days of discontinuation of dosing with nivolumab or 30 days of discontinuation with NKTR-214 or other chemotherapeutic agents will

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be reported to Nektar Therapeutics Drug Safety within **24 hours** of when the site becomes aware of the event. Unlike the AE reporting period which ceases upon initiation of new antineoplastic therapy, SAEs, regardless of causality attribution, should continue to be reported through this observation period regardless of whether new antineoplastic therapy has been initiated.

In addition, SAEs that occur after 100 days of discontinuation of dosing with nivolumab or ipilimumab, or 30 days of discontinuation with NKTR-214 or other chemotherapeutic agents and are assessed by the Investigator as possibly related or related to study drug(s) will also be reported to Nektar Therapeutics Drug Safety within **24 hours** of when the site becomes aware of the event.

SAEs must be reported to Nektar Therapeutics Drug Safety via email or Safety Fax as listed at the beginning of this protocol.

The Investigator must complete the SAE Report Form, assess the causality relationship to the study treatment as applicable, and send the completed SAE form via email or fax to Nektar Therapeutics Drug Safety. A follow-up report and any additional records (such as hospital records, consultant reports, and autopsy findings) will be emailed or faxed to Nektar Therapeutics Drug Safety within **24 hours** of receipt. Any medication or other therapeutic measures used to treat the event will be recorded.

All SAEs will be followed as described in Section 7.8.

Reporting of SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be done in accordance with the standard operating procedures (SOPs) and policies of the IRB/IEC. Adequate documentation must be provided to Nektar Therapeutics, showing that the IRB/IEC was properly notified. Serious AEs will be reported by Nektar Therapeutics or designee to the Regulatory Authorities, per local regulations.

7.8 Serious AE Follow-up

All study treatment-related SAEs that have not resolved by the EOT visit (Section 5.4) will be followed until any of the following occur (whichever comes first):

- The event resolves.
- The event has stabilized.
- The event returns to baseline, if a baseline value is available.
- It is unlikely that any additional information can be obtained (e.g., patient or health care practitioner refuses to provide additional information; lost to follow-up after demonstration of due diligence with follow-up efforts).
- The patient dies or is lost to follow-up.

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All ongoing SAEs assessed as "unrelated" to study drug(s) will be followed until resolution or until the EOT visit (Section 5.4), whichever is earlier. In the case where an unrelated SAE has not completely resolved by the EOT visit, the final outcome of these ongoing SAEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

7.9 Disease Progression – Not Reportable as an AE

It is anticipated that during this study a proportion of patients will experience disease progression prior to study discontinuation. PD in some patients may result in hospitalization or death. Hospitalization or deaths that are attributed by the investigator solely to disease progression are not considered to be adverse events.

If there are separate identifiable clinical manifestations of the disease progression that the investigator is unsure that the events are attributed solely to disease progression, e.g., pleural effusion or weight loss, these manifestations are reportable as AEs. Such an event should be recorded on the AE case report form (CRF) and, if the event meets any of the "serious" criteria, it must also be reported on the SAE form.

7.10 Immune-mediated Adverse Event and AEs of Special Interest Reporting

imAEs, such as those characteristic of checkpoint inhibitors, are considered AEs of special interest due to their potential clinical significance. Nektar has instituted a rigorous internal review process and adjudication by the Drug Safety Committee to evaluate imAEs associated with either NKTR-214, nivolumab, and/or ipilimumab. Investigators should use clinical judgment characterizing an AE as immune mediated, including the requirement for steroid treatment, and are encouraged to rule out neoplastic, infectious, metabolic, toxic, or other etiologies to the extent possible, before characterizing an event as immune mediated.

In addition, the following adverse events are considered "adverse events of special interest" (AESI). These AESIs regardless of the seriousness are required to be reported within 24 hours from the sites to Nektar Drug Safety: pharmacovigilance@nektar.com:

- Hypotension Grade ≥ 3
- Syncope Grade ≥ 3
- Infusion related reaction Grade ≥ 3
- Cytokine release syndrome Grade ≥ 3
- Capillary leak syndrome (any grade)
- Pulmonary edema (any grade)
- Hypereosinophilic syndrome (any grade)
- Qualifying drug-induced liver injury (DILI)

Potential drug induced liver injury is defined as:

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1) Treatment-emergent ALT or AST > 3 times baseline value

AND

2) Total bilirubin > 2 times ULN or clinical jaundice, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of elevated liver enzymes and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug (s) known to be hepatotoxic.

7.11 Pregnancy

The Sponsor must be notified within 24 hours of the initial report and any follow-up reports of a male patient's female partner or a female patient becoming pregnant during the course of the study and for 5 months after the last dose of the study drug(s) via the Pregnancy Notification Form. Pregnancy, although reportable, is not considered an AE/SAE unless a female patient or male patient's female partner experiences signs or symptoms of pregnancy complications; however, the contact information for pregnancy reporting is the same as for SAE reporting and listed in Section 7.7. Female patient(s) who become pregnant will be followed until the outcome of the pregnancy is known. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring.

If a female patient becomes pregnant, administration of the study drug(s) must be discontinued immediately.

7.12 Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Events (Section 1.2). Clinical laboratory tests will be performed by the local laboratory for Part 1 and Part 3 and central laboratory for Parts 2 and 4 (except as designated in Appendix 1). (For Parts 2 and 4, if the central laboratory tests are cancelled, lost, or considered inadequate for analysis, the site may forward an identical set of local laboratory samples for eligibility review. Central laboratory testing must be repeated prior to the first dose of study drug. If local laboratory results are determined to be acceptable by the Medical Monitor [or designee] during eligibility review, enrollment may proceed.) Clinical laboratory test data will be reviewed by the Investigator or qualified Sub-Investigator. Additional clinical laboratory tests may be ordered at the Investigator's or qualified Sub-Investigator's discretion. Additional testing for PK and biomarkers will be performed by the designated central laboratory.

The Investigator or qualified Sub-Investigator will review all laboratory results for clinical significance. Any laboratory result deemed clinically significant (i.e., is associated with signs

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and symptoms, requires treatment, or requires follow up) will be recorded as an AE as described in Section 7.1.

7.13 Physical Examinations

Physical examinations should be conducted according to the Schedule of Events (Section 1.2). Full physical examinations should be conducted at screening, Day 1 of each cycle, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms.

7.14 Vital Signs

Vital sign measurements will be recorded according to the Schedule of Events (Section 1.2). Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation (oxygen saturation on dosing days only), and temperature. It is preferred that the same arm be used for all blood pressure readings, if possible. Instructions for more frequent vital sign monitoring after completion of study drug administration are provided in Section 5.3.7.1. Weight is to be reported at each vital sign visit, height at screening visit only.

7.15 Electrocardiograms

Prior to each NKTR-214 PK sampling time in Cycle 1 of treatment, 5 minutes of ECG data will be recorded (see Appendix 2 Schedule of Assessments).

Patients must be resting quietly in the supine position for at least 5 minutes before the ECG collection. Five-minute ECG will be performed on a calibrated 12-lead machine and the 5-minute recording will be converted into a summary ECG (simulated 10-second ECG). The summary ECG will be submitted to a designated ECG laboratory for interpretation of ECG and interval duration measurements. Interpretation of ECGs and interval duration measurements will be provided to the site.

The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant will be reported as an AE as described in Section 7.1.

7.16 Echocardiograms

Standard echocardiogram will be performed to assess cardiac function and LVEF according to the Schedule of Events (Section 1.2). In the event of an abnormal ECHO, the Investigator may perform a stress ECHO (either exercise or nuclear). A MUGA scan can be performed to assess cardiac function and LVEF if a standard echocardiogram cannot be performed. The same assessment method should be used for the same patient throughout the study. After a number of

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patients have been enrolled in the dose escalation, the Safety Review Committee may determine that an ECHO is not needed, in this case the ECHO assessment may be removed from study.

7.17 Pregnancy Tests

Serum pregnancy tests will be performed on women of childbearing potential during screening. Urine or serum pregnancy tests will be performed on women on Day 1 of each cycle prior to dosing and at EOT. A negative pregnancy test result must be obtained before the administration of the study drug(s).

A pregnancy test does not need to be performed on women who are postmenopausal for at least 1 year or surgically sterile for at least 5 months before signing the ICF.

If a female patient becomes pregnant, administration of the study drug(s) must be discontinued immediately. Requirements for reporting a pregnancy are provided in Section 7.11.

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8.0 ASSESSMENT OF EFFICACY EVALUATIONS

Response and progression will be determined using RECIST 1.1 (Eisenhauer, 2009).

8.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

8.1.1 Measurable Disease

Target tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm); when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

8.1.2 Non-measurable Disease

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes ≥ 10 to < 15 mm in short axis) as well as truly non-measurable lesions, are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by reproducible imaging techniques.

8.2 Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

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Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). When lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study. For cutaneous lesions that are included in target lesions, digital photographs should be obtained and utilized for measurement.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. If a slice thickness > 5 mm is used for CT scanning, then the minimum longest diameter for a target lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the ULN, however, they must normalize for a patient to be considered in complete response.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases when the nature of a residual lesion is in question. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

8.2.1 Tumor Response Evaluation

8.2.1.1 Assessment of Overall Tumor Burden at Baseline and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

8.2.1.2 Baseline Documentation of 'Target' and 'Non-target' Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means that in instances where patients have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions, respectively, will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but

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< 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'.

8.2.1.3 Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, if the lesion is believed to be present and is faintly seen but is too small to measure with any accuracy, a default value of 5 mm should be assigned.

8.2.2 Response Criteria using RECIST 1.1

8.2.2.1 Evaluation of Target Lesions

Table 19 provides the definitions of the criteria used to determine objective tumor response for target lesions.

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Table 19: Criteria to Determine Objective Tumor Response for Target Lesions per RECIST 1.1

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameters (SLD) of target lesions, taking as reference the baseline SLD
Progressive Disease (PD)	At least a 20% increase in the SLD of target lesions, taking as reference the smallest SLD on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm relative to nadir. (Note: the appearance of one or more new lesions is considered progression.)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

8.2.2.2 Evaluation of Non-Target Lesions

Table 20 provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points of radiographic assessments.

Table 20: Criteria to Determine Tumor Response for Non-Target Lesions per RECIST 1.1

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).[a]

NOTE: If tumor markers are assessed for a given patient and are initially above the ULN, they must normalize for a patient to be considered in complete CR.

a. In this setting, when a patient has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in the non-target disease such that, even in the presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare (from Section 4.3.4 of RECIST 1.1).

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8.2.2.3 Confirmatory Measurement/Duration of Response

8.2.2.3.1 Confirmation

Confirmation of response (either PR or CR) is required. Changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥ 4 weeks after the criteria for response are first met.

8.2.2.4 Evaluation of Overall Response Using RECIST 1.1

Table 21: Best Overall Response When Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise. PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise. PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise. NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise. PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise. NE
NE	NE	NE

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease

a. If a CR is truly met at the 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 (7 weeks) 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

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9.0 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.1 General Considerations

In general, continuous data will be summarized by descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of patients. Unless otherwise specified, data collected during the dose escalation/schedule finding phase (Parts 1 and 3) will be summarized by dose cohort, and data collected during the dose expansion phase (Parts 2 and 4) will be summarized by tumor type.

All efficacy endpoints except overall survival will be analyzed using the response evaluable population. Certain efficacy endpoints will also be summarized for all treated patients as sensitivity analyses. All safety endpoints will be summarized using the safety population.

A description of analysis methods and detailed definitions for efficacy and safety endpoints will be provided in the statistical analysis plan (SAP).

9.2 Determination of Sample Size

During Part 1, cohorts of at least 3 patients will be treated at each dose level. Additional patients will be added to each dose cohort based on the scheme and rules outlined in Section 5.3.2 or Sponsor determination of the need for additional data to further evaluate the benefit/risk profile. It is estimated that approximately 50 patients will be enrolled into the Part 1 dose escalation phase.

[redacted]

During Parts 2 and 4, patients will be enrolled as described in Sections 5.3.4 and 5.3.6. The sample size is strictly based on efficacy, specifically based on the target ORR relative to historic response rate. The Fleming 2-stage design (Fleming, 1982) framework will be used as a guide for the tumor cohorts. The total sample size for each expansion cohort (including patients treated at the RP2D during the dose escalation period) will be 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 22 and Table 23). The historic and target response rate assumptions may change over time and may need to be adjusted at the time of response data from this study are available. The 2-stage design provides an option to stop early for futility as well as allowing an early start for Phase 3

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preparation if a strong antitumor activity signal is observed. However, the final decision will be based on the totality of overall treatment effect for multiple study endpoints and their associations with the tumor response rate. Enrollment may continue into Part 2 while the planned number of patients for Part 1 are followed for efficacy-evaluable tumor assessments. There will be no stopping of enrollment to a tumor cohort for efficacy, although early planning for the next stage of clinical development may be initiated.

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Table 22: True (Target) and Historic Objective Response Rate for Each Indication in Part 2

Cohort	Indication	Objective Response Rate (%)		Sample Size[a]			Futility		Efficacy		Reference for Historical ORR Assumption
		Historical	Target	N1	N2	Total	S1	S2	T1	T2	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2a	RCC 1L	25	50	11	15	26	≤ 2	≤ 9	≥ 6	≥ 10	Topalian, 2012
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 22: True (Target) and Historic Objective Response Rate for Each Indication in Part 2

Cohort	Indication	Objective Response Rate (%)		Sample Size[a]			Futility		Efficacy		Reference for Historical ORR Assumption
		Historical	Target	N1	N2	Total	S1	S2	T1	T2	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]
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Table 22: True (Target) and Historic Objective Response Rate for Each Indication in Part 2 (Contd)

Cohort	Indication	Objective Response Rate (%)		Sample Size[a]			Futility		Efficacy		Reference for Historical ORR Assumption
		Historical	Target	N1	N2	Total	S1	S2	T1	T2	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: cis = cisplatin; CRC = colorectal carcinoma; EGFR = epidermal growth factor receptor; HR = hormone-receptor positive; I-O = immuno-oncology; L = line; MEL = melanoma; MSI = microsatellite instability; NA = not available; ORR = objective response rate; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SCLC = small-cell lung cancer; TNBC = triple-negative breast cancer

a. 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%).

[redacted]

[redacted]

Approximately 925 patients will be enrolled into Part 2. Additional patients may be added to selected expansion cohorts to further evaluate the benefit/risk profile.

[redacted]

[redacted]

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Table 23: True (Target) and Historic Objective Response Rate for Each Indication in Parts 3 and 4

[redacted]	[redacted]		[redacted]			[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

9.3 Safety Monitoring

A Safety Review Committee consisting of representatives from the Sponsor's Clinical Development, Drug Safety, Biostatistics, other functional representatives, as needed, and at least one site Investigator will meet at least quarterly to review safety data for potential safety risks or more frequently if needed. The Safety Review Committee will be convened to make a recommendation on the continuation, modification, or discontinuation of the study.

9.4 Replacement of Patients

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

9.5 Analysis Sets

Safety Population/All treated Population: All patients who receive at least 1 dose (or partial dose) of study drug will be included in the analysis of safety.

DLT Population: All patients who complete at least the DLT observation period or discontinue from the study treatment due to DLT will be included.

Pharmacokinetic Population: All patients in the Safety Population who have evaluable analyte concentration-time profiles that allow for the computation of meaningful PK parameter values.

Response Evaluable Population: Patients who have measurable disease (per RECIST 1.1) at baseline and also have at least one post-baseline assessment of tumor response and (for Parts 2 and 4) meet eligibility criteria are response evaluable.

Modified Response Evaluable Population: Eligible patients (for Parts 2 and 4) who have measurable disease (per RECIST 1.1) at baseline and also have one post-baseline assessment of tumor response or are withdrawn due to progressive disease/death prior to first response assessment.

9.6 Planned Analyses

9.6.1 Demographics and Baseline Characteristics

Demographic data (age, sex, ethnicity, body weight) and baseline disease characteristics will be tabulated and summarized by dose cohort (for Parts 1 and 3) and by tumor type (for Parts 2 and 4) and presented in data listings.

9.6.2 Safety

The primary endpoints of the study are to determine the MTD of NKTR-214 in combination with nivolumab and in combination with nivolumab and ipilimumab. Safety assessments will be summarized separately for Parts 1 through 4. AEs and toxicity will be evaluated according to NCI CTCAE version 4.03. Safety assessments will be performed by medical review of AEs and laboratory results.

The incidence rate of DLTs will be evaluated by dose cohort for the DLT population.

Treatment emergent AEs (TEAEs) will be summarized by preferred term, system organ class, NCI-CTCAE grade of severity, and relationship to the study treatment.

A TEAE is defined as: (regardless of intensity)

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

Vital signs (including change in weight) and clinical laboratory test results will be summarized descriptively by dose (for Parts 1 and 3) and by tumor type (for Parts 2 and 4). Any significant physical examination findings will be listed. ECG data will be evaluated by central review and abnormalities, if present, will be listed. A separate listing and summary of all imAEs will be provided. A listing and summary of patients who discontinued study drug(s) due to an AE will be provided.

A data listing for deaths will be provided.

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9.6.3 Efficacy

Efficacy analyses will be performed on data provided by the Investigator sites as well as from an independent radiology review for the following efficacy outcomes:

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

The primary efficacy measurement is the ORR per RECIST 1.1 based on data provided by the Investigator's assessment using the response evaluable population. The number and percentage of patients with CR or PR as their best overall response will be calculated. The 95% confidence interval (CI) will be calculated using the exact binomial method. In addition, the ORR analysis will be performed on the number of patients treated. All tumor assessments and response data will be listed. The BOR will be summarized similarly using the response evaluable population.

The TTR will be defined for patients who had confirmed CR or confirmed PR as the time from the date of first dose to date of first documented CR or PR. TTR will be summarized using descriptive statistics.

DOR will be defined for patients who have confirmed CR or confirmed PR as the date from first documented CR or PR to the date of the first objectively documented disease progression per RECIST 1.1 or death due to any cause, whichever is earlier. Patients who do not have disease progression per RECIST 1.1 will be censored on the date of last evaluable tumor assessment. Patients who started any subsequent antineoplastic regimen, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent antineoplastic regimen. The DOR will be estimated using the Kaplan-Meier method. The 25%, median and 95% CI, and 75% quartiles will be summarized.

CBR, defined as the number of patients with confirmed CR, confirmed PR, or SD (≥ 7 weeks), will be summarized similarly to ORR using the response evaluable population and all treated patients. Additionally, CBR at 16 weeks (CBR16) and CBR at 24 weeks (CBR24), defined as confirmed CR, confirmed PR, or SD for ≥ 16 weeks or ≥ 24 weeks, respectively, will be summarized.

PFS is defined as the time from the date of first dose to the date of the first objectively documented progressive disease per RECIST 1.1 or death, whichever earlier. For patients who

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do not have date of disease progression per RECIST 1.1 and date of death, patients will be censored on the date of last evaluable tumor assessment. For patients who started a new antineoplastic regimen prior to disease progression per RECIST 1.1, patients will be censored on the date of last evaluable tumor assessment prior to receiving the new antineoplastic regimen. For patients whose disease progression or death appears after missing two consecutive tumor assessments, patients will be censored on the date of last evaluable tumor assessment. Patients who are lost to follow up will be censored on the date of their last evaluable tumor assessment.

PFS will be estimated using the Kaplan-Meier method. The 25%, median and 95% CI, and 75% quartiles will be summarized using all treated patients.

OS will be defined as the date of first dose to the date of death. Patients who do not have a date of death will be censored on the last date for which a patient was known to be alive. OS will be analyzed similarly to PFS.

9.6.4 Immunogenicity

Validated assays will be used for the determination of anti-drug antibodies to NKTR-214 and related components, nivolumab, and ipilimumab in human serum. Only patients who receive at least 1 dose of NKTR-214, nivolumab, and/ or ipilimumab and who provide at least 1 post-treatment sample will be evaluated. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable anti-drug antibodies. Samples confirmed positive may also be evaluated for neutralizing antibody activity. Anti-drug antibodies to NKTR-214, nivolumab, and ipilimumab will be analyzed according to a prespecified analysis plan.

9.6.5 Exploratory Analyses

The responses based on irRECIST will be evaluated as an exploratory endpoint. In addition, characterization of immune system biomarkers in predose blood and tumor biopsies, as well as changes in immune system biomarkers after treatment with study drugs and their relationship with efficacy, will be exploratory endpoints. Samples may be used for additional research purposes related to the development of NKTR-214.

9.6.6 Pharmacokinetics

Plasma concentrations of NKTR-214 and its metabolites, and serum concentrations of nivolumab and ipilimumab, will be measured using validated method(s). Before analysis of samples, assay sensitivity, specificity, linearity, and reproducibility will be determined. Pharmacokinetic parameters such as maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the curve (AUC), clearance (CL), volume of distribution (V_d), and half-life ($t_{1/2}$) will be estimated from concentration-time data where possible. Pharmacokinetic data from this study may also be pooled with data from other clinical studies for the purpose of PK modeling. Pharmacokinetic parameters will be tabulated and summarized with descriptive statistics. Select pharmacokinetic parameter values will be correlated with select safety and response measurements for assessment

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of exposure-response relationships. Data from patients prematurely ending participation in the study may be excluded from the PK data evaluation.

9.7 Concomitant Medications

All reported concomitant medications will be mapped using the World Health Organization Drug Dictionary. Concomitant medications will be tabulated in summary tables and data listings.

9.8 Missing Data

Statistical considerations and methodology for handling missing data will be detailed in the Statistical Analysis Plan.

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10.0 STUDY OR STUDY SITE TERMINATION

The Sponsor has the right to suspend or terminate the study or part of the study at any time for any reason.

If an Investigator suspends or terminates their study site, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations.

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11.0 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

11.1 Changes to the Protocol

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/Independent Ethics Committee (IEC), except when necessary to eliminate immediate hazards to the patient or when the change(s) involve only logistical or administrative aspects of the study. Any deviation may result in the patient having to be withdrawn from the study and rendering that patient nonevaluable. All protocol deviations and the reasons for such deviations are to be documented in the source documents and reported to the Sponsor.

Prior to formal protocol amendment, an administrative letter describing protocol changes may be used by the Sponsor where permitted. The administrative letter will include a commitment to amending the protocol within a specified time frame and, following approval by the IRB/IEC, will eliminate the requirement to document a protocol deviation for the described change.

11.2 Monitoring

In accordance with Code of Federal Regulations 21 CFR 312.56, International Conference on Harmonisation (ICH) GCP, and local regulations, the clinical monitor will periodically inspect all **electronic case report forms (**eCRFs**)**, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR 312 Subpart D (Responsibilities of Sponsors and Investigators), ICH GCP, and local regulations, the monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs; ensure that all protocol requirements, applicable FDA, ICH GCP, and local regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the Investigator, including, but not limited to, medical records (office, clinic, or hospital) for the patients in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor. The Investigational New Drug Application (IND) regulations and ICH E6 guidelines also require the Investigator to allow authorized representatives of the Sponsor, IRB/IEC, FDA, and other relevant regulatory authorities direct access to study source records, and to inspect and make copies of the same records. The names and identities of the patients need not be divulged to the Sponsor; however, the records must nevertheless be available to be inspected for review. This can be accomplished by blacking out the patient's name and replacing the name with the patient's study identification number. If these requirements are in conflict

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with local regulatory restrictions or institutional requirements, the Investigator must inform the Sponsor of these restrictions before initiation of the study.

11.3 Direct Access to Source Data/Documents for Audits and Inspections

Members of the Sponsor or designees may conduct monitoring and auditing activities of a clinical site at any time during or after completion of the study. The Investigator will be informed of such activities.

Representatives of the FDA or other regulatory agencies, including IRB/IEC representatives, may also conduct an inspection or perform an audit of the study. The investigator(s)/institution(s) will permit trial-related audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents and study records. If informed of such an inspection, the Investigator should notify the Sponsor immediately. The Investigator will ensure that the inspectors and auditors have access to the clinical supplies, study site facilities, and laboratory, and that all data (including original source documentation) and all study files are available, if requested.

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12.0 ETHICS

This study will be conducted to be consistent with the principles that have their origin in Declaration of Helsinki and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with the current ICH GCP guidelines (ICH E6), as well as with any applicable regulatory authority, federal, state and/or local laws and regulations.

12.1 IRB/IEC Approval

Before enrollment of patients into the study, as required by FDA regulations (21 CFR § 56), ICH GCP, applicable regulatory authority requirements, and local regulations, the current protocol and ICF will be reviewed and approved by an appropriate IRB or IEC. A letter documenting the IRB or IEC approval must be received by the Sponsor before the initiation of the study at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator, Sponsor, or designee will submit a progress report at least once yearly to the IRB or IEC. However, the frequency of these reports will depend on IRB or IEC requirements. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB or IEC per the IRB or IEC requirements, and in compliance with FDA regulations, applicable regulatory authority requirements, and ICH GCPs.

The Investigator, the Sponsor, or designee shall notify the IRB or IEC of any SAEs, suspected unexpected serious adverse reactions (SUSARs), or any other information that may affect the safe use of the study drug(s) during the study, per the IRB or IEC local requirements, and in compliance with FDA regulations, country and local regulatory authority regulations, and ICH GCPs.

12.2 Written Informed Consent

Written documentation of informed consent must be obtained from each patient or legal representative before entering the study. Patients will be informed of the nature of the study, and the ICF must be presented to each patient in the language in which the patient is fluent.

Informed consent will be obtained from and documented for each patient prior to the conduct of any protocol-specific procedures. Signed and dated ICFs will be retained by the Investigator with the study records. Each patient will be given a copy of the signed and dated ICF.

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13.0 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection Instruments and Source Documents

13.1.1 Study Records

During the study, the investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. The investigator/institution should, at a minimum, maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 section 8) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

13.1.2 Data Collection Instruments

Data collection instruments (DCIs) (e.g., eCRFs, electronic clinical outcomes assessments [eCOA], and paper forms) will be used in this study. These instruments are used to transmit the information collected during the performance of this study to the Sponsor or Sponsor's designee and regulatory authorities. The Investigator must review the DCIs for completeness and accuracy and must approve all data, including any changes made. Furthermore, the Investigator retains full responsibility for the appropriateness and accuracy of all data collected in the DCIs.

13.2 Retention of Essential Documents

For sites in the US: All records and documents pertaining to the study including, but not limited to, those outlined above will be maintained by the Investigator for a period of at least 2 years after FDA approval of the drug or at least 2 years after withdrawal of the IND under which this study was conducted, whichever is longer.

For sites outside the US: Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution when these documents no longer need to be retained.

To avoid any possible errors, the Investigator will contact the Sponsor before transferring or destroying any study records. The Investigator will also promptly notify the Sponsor in the event of accidental loss or destruction of any study records.

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13.3 Confidentiality

Patient confidentiality will be maintained per local legal and regulatory requirements and applicable US federal regulations and ICH GCP guidelines. To comply with GCP guidelines and requirements, patient records will be reviewed during monitoring visits and audits conducted by the Sponsor, Sponsor's representatives, or health authorities. During these activities, every reasonable effort will be made to keep medical information, including patient identifying information, as confidential as possible as required by law.

13.4 Security Measures

Sites will employ both technical and organizational measures (such as, but not limited to, controlling access to personal patient data to only those with a need to know such data, data encryption, data anonymization and pseudonymization, and so forth) to ensure patient and patient data privacy. Sites will adhere to a “privacy by design” and “privacy by default” approach in collecting, storing, and processing personal patient data.

In the event of a breach of the security measures used by the Site to ensure patient and patient data privacy, the Site will immediately notify the Sponsor.

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14.0 PUBLICATION POLICY

All data are the property of the Sponsor. Any formal presentation or publication of data from this study will be considered for joint publication by the Sponsor personnel and Investigator(s).

The Investigator may be required to sign the clinical study report if it is to be used in a registration submission to the health authorities of some countries.

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APPENDIX 1: CLINICAL LABORATORY TESTS

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Chemistry</th><th>Serology</th></tr>
<tr><td rowspan="4">• Hemoglobin (Hgb)
• Hematocrit (HCT)
• Red blood cell (RBC) count
• Platelet count
• White blood cell (WBC) count
• Neutrophils
• Lymphocytes
• Monocytes
• Eosinophils
• Basophils
• Mean corpuscular volume (MCV)
• Mean corpuscular hemoglobin (MCH)
• Mean corpuscular hemoglobin concentration (MCHC)</td><td rowspan="4">• AST (SGOT)
• ALT (SGPT)
• Alkaline phosphatase (ALP)
• Gamma-glutamyl transferase (GGT)
• Albumin
• Creatinine
• Calculated creatinine clearance
• Calcium
• Glucose
• Total protein (TP)
• Total bilirubin
• Sodium
• Potassium
• Chloride
• CO_2 content or bicarbonate
• Blood urea nitrogen (BUN)
• Lactate dehydrogenase (LDH)
• Uric acid</td><td>• Hepatitis B surface antigen (HBsAg)
• Hepatitis C virus antibody (anti-HCV)
• Human immunodeficiency virus (HIV) antibody</td></tr>
<tr><td>Additional Labs</td></tr>
<tr><td>• Creatine kinase
• Thyroid stimulating hormone (TSH)
• Free thyroxine (T4)
• Free or total triiodothyronine (T3)
• Lipase
• Amylase
• Serum pregnancy (HCG)</td></tr>
<tr><td>Coagulation</td></tr>
<tr><td></td><td></td><td>• Partial thromboplastin time (PTT)
• Prothrombin time (PT)</td></tr>
<tr><th colspan="3">Urinalysis</th></tr>
<tr><td colspan="2">• Specific gravity
• pH
• Glucose
• Protein
• Bilirubin
• Ketones
• Leukocyte esterase
• Blood</td><td>For positive protein, white blood cell or blood, a microscopic examination including:
• Red blood cells
• White blood cells
• Epithelial cells
• Bacteria
• Crystals
• Casts</td></tr>
</table>

Local laboratory will be used for Part 1 and Part 3; central laboratory will be used for Part 2 and Part 4.

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APPENDIX 2: SCHEDULE OF ELECTROCARDIOGRAM, VITAL SIGNS, PHARMACOKINETICS, BIOMARKER, AND IMMUNOGENICITY SAMPLE ASSESSMENTS

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Appendix 2 Table 1: Part 2 - Assessment Schedule for NKTR-214 + Nivolumab

Event		Screening[a]	Cycle 1				Cycle 2		Cycle 3 and Beyond		Post-treatment
		Day -28 to -1	Day 1[b]	Day 2	Day 3	Day 8	Day 1[b]	Day 8	Day 1[b]	Day 8 (Cycles 5, 7, 13 and 17 only)	EOT & Follow-up
Predose		VS	VS[c]	VS[c] (once)	VS[c] (once)	VS[c] (once)	VS	VS[c] (once)	VS	VS[c] (once)	VS[c] (EOT only)
		ECG	ECG[d] + PK-214				PK-214		PK-214		
			PK-nivo						PK-nivo (only Cycles 3, 8, 16, 24, 36)		
			BM			BM[e]	BM	BM[e]	BM (only Cycles 5, 7, 13 and 17)	BM[e]	
			IG-214				IG-214		IG-214 (only on odd-number cycles – Cycles 3, 5, 7, etc.)		IG-214 (EOT and at the first 3-month follow-up visit)
			IG-nivo						IG-nivo (Cycles 3, 8, 16, 24, 36)		
T=00:00 hr	Start of 30 min NKTR-214 Infusion (SOI)		214 Infusion				214 Infusion		214 Infusion		
T=00:30 - 01:00	Within 30 min of the end of 214 infusion and before Nivolumab (Nivo) infusion		ECG[d] + PK-214[f]				PK-214		PK-214		
			Serum for complement activation								
T=01:00 - 01:30[g]	Nivo Infusion[g]		Nivo Infusion				Nivo Infusion		Nivo Infusion		
T=01:30 - 2:00	End of Nivo Infusion		PK-nivo								
T=03:00 (± 30 min) SOI			ECG[d] + PK-214[f]								
T=03:00 SOI or 1 hour following the end of nivo infusion			VS				VS		VS		
T=06:00 + 2 hrs SOI			ECG[d] + PK-214[f]								
T=48:00 ± 4 hrs SOI					ECG[d] + PK-214[f]						
T=168:00 ± 4 hrs SOI						ECG[d] + PK-214[f]					

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Abbreviations: VS = vital signs; ECG = electrocardiogram; BM = Blood Biomarker samples; SOI = Start of NKTR-214 infusion; Nivo = Nivolumab; PK-214 = blood samples for pharmacokinetic (PK) analyses of NKTR-214 and its metabolites; PK-nivo = blood samples for PK analyses of nivolumab; IG-214 = immunogenicity samples for NKTR-214; IG-nivo = immunogenicity samples for nivolumab

Footnotes:

a. All assessments are done at any time during the Screening Period and all other Screening assessments are outlined in the Schedule of Events (Section 1.2).

b. Study drug infusion is expected to occur on Day 1 of each cycle, however, if dosing occurs on a different day, all assessments should be adjusted based on the study drug infusion dosing schedule.

c. Vital Signs –vital signs are to be monitored and recorded at any time during the visit on Days 2, 3, 8, 11 and at EOT.

d. ECG - Prior to each NKTR-214 PK sampling time in Cycle 1 of treatment, 5 minutes of ECG data will be recorded. Patients must be resting quietly in the supine position for at least 5 minutes before the ECG collection.

e. Biomarkers - Biomarkers may be collected at any time on Day 8.

f. PK-214 - All NKTR-214 PK assessments following the study drug infusion(s) should be referenced from the start of NKTR-214 infusion (SOI).

g. Nivo infusion - It is highly recommended that nivolumab infusion start within 30 minutes after completion of NKTR-214 infusion. The time tracking in the above table assumes that the nivolumab infusion starts 30 minutes after the end of NKTR-214 infusion.

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Appendix 2 Table 2: Parts 3/4, Cohort A ([redacted]

[redacted]

Tannir NM, *et al. J Immunother Cancer* 2022; 10:e004419. doi: 10.1136/jitc-2021-004419

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Event	[redacted]	[redacted]					[redacted]			[redacted]		[redacted]
[redacted]		[redacted]										
[redacted]		[redacted]					[redacted]					
[redacted]		[redacted]					[redacted]			[redacted]		
[redacted]		[redacted]										
[redacted]		[redacted]										
[redacted]		[redacted]					[redacted]					
[redacted]				[redacted]				[redacted]				
[redacted]					[redacted]				[redacted]			

[redacted]

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Appendix 2 Table 2: Parts 3/4, Cohort B ([redacted]

[redacted]

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[redacted]

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i. [redacted]

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