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:	11 February 2020
Protocol Amendment No.	7.0
Supersedes:	Amendment 6.0 dated 18 June 2018 Amendment 5.1 dated 09 January 2018 Amendment 5.0 dated 05 December 2017 (US) Amendment 4.0 dated 22 June 2017 (Canada, Belgium, Ukraine, US) Amendment 3.2 dated 07 August 2017 (France)
US IND Number:	125471
EudraCT Number:	2016-003543-11
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA
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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:	11 February 2020
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**

PROTOCOL APPROVAL PAGE

A Phase 1/2, Open-label, Multicenter Study of the Combination of NKTR-214 and Nivolumab or the Combination of NKTR-214, Nivolumab, and Other Anti-Cancer Therapies in Patients with Select Locally Advanced or Metastatic Solid Tumor Malignancies

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Signing Reason: I approve this document
Signing Time: Feb-19-2020 | 5:16:58 PM PST
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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
AEC	absolute eosinophil count
AESI	adverse event of special interest
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
BRAF	proto-oncogene B-Raf
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
CVA	cerebrovascular accident
D5W	dextrose 5% in water for injection
DCI	data collection instrument

Abbreviation or Term	Definition
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
dMMR	mismatch repair deficient
DOR	duration of response
DWI	diffusion-weighted imaging
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 receptor 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

Abbreviation or Term	Definition
I-O	immuno-oncology
IRB	institutional review board
irRECIST	immune-related RECIST
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
N1	sample size at stage 1
N2	sample size at stage 2
NCI	National Cancer Institute
NKTR-214	bempegaldesleukin (International Nonproprietary Name)
NKTR-214/nivolumab/ipilimumab	triplet containing NKTR-214 and nivolumab and ipilimumab
NE	non-evaluable
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

Abbreviation or Term	Definition
PD-L1	programmed cell death ligand 1
PEG	polyethylene glycol
PFS	progression-free survival
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
S1	futility boundary at stage 1
S2	futility boundary at stage 2
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
T1	efficacy boundary at stage 1
T2	efficacy boundary at stage 2
$T_{1/2}$	terminal elimination phase half-life
T3	triiodothyronine
T4	free thyroxine
TEAE	treatment-emergent adverse event

Abbreviation or Term	Definition
TIL	tumor infiltrating lymphocyte
TIA	transient ischemic attack
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
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
WFI	Water for Injection

1.0 STUDY SYNOPSIS

Name of Sponsor:	Nektar Therapeutics
Name of Finished Products:	Bempegaldesleukin (NKTR-214 drug product) Opdivo® Yervoy® Abraxane® Paraplatin® Platinol® Alimta® Halaven® Taxol®
Name of Active Ingredients:	NKTR-214 drug substance Nivolumab (anti-PD-1) Ipilimumab (anti-CTLA-4) Nab-paclitaxel (nanoparticle albumin-bound paclitaxel) Carboplatin Cisplatin Pemetrexed (folate antimetabolite) Eribulin mesylate (nontaxane, microtubule dynamics inhibitor) Paclitaxel
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)

	
Study Population:	Adults aged 18 years and older with select locally advanced or metastatic solid tumor malignancies who have measurable disease. Melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), urothelial carcinoma, triple-negative breast cancer (TNBC), hormone-receptor-positive breast cancer, gastric cancer, colorectal cancer (CRC), or small cell lung cancer (SCLC).
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 936 patients will be enrolled. Part 3 (schedule finding: NKTR-214 plus nivolumab plus ipilimumab): Approximately 36 patients will be enrolled. Part 4 (dose expansion: NKTR-214 plus nivolumab plus ipilimumab): Approximately 106 patients will be enrolled.
Number of Study Sites:	Approximately 75 sites
Countries:	Part 1: US Part 2: US, Canada, Europe, Australia, and Hong Kong; additional countries may be added Part 3: select sites in US Part 4: select sites in US

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. There were no Grade 3 TRAEs in the 25 patients treated at 0.006 mg/kg NKTR-214 with nivolumab 360 mg flat dose q3w. 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, 21 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. 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 936 patients will be enrolled in the cohorts specified in the table below.

Part 2 is closed to patient screening and enrollment under Amendment 7.

Part 2 Cohorts: All Patients Receive NKTR-214 plus Nivolumab[a]

Indication	Cohort	Description
Melanoma	1a[b]	1L
	1b[b]	2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory
	1c[c]	2L, BRAF wild type anti-PD-1 or anti-PD-L1 relapse/refractory
	1d[c]	1L, following prior adjuvant therapy
	1e	Patients enrolled under an earlier protocol version who are no longer eligible for Cohorts 1a to 1d
RCC	2a[b]	1L
	2b[c]	2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory
	2c	Patients enrolled under an earlier protocol version who are no longer eligible for Cohorts 2a or 2b
NSCLC	3a.1[f]	1L, PD-L1< 1%
	3a.2[f]	1L, PD-L1 ≥ 1% - < 50%
	3a.3[f]	1L, PD-L1 ≥ 50%
	3a.4[f]	1L, PD-L1 status unknown
	3b[d]	2L, I-O therapy-naive following platinum-based therapy
	3c[c]	2L-3L, anti-PD-1 or anti-PD-L1 relapse/refractory
	3d.1[f]	1L, nonsquamous in combination with platinum/pemetrexed (+ maintenance pemetrexed)
	3d.2[f]	1L, nonsquamous in combination with platinum/pemetrexed (no maintenance pemetrexed)
	3e[f]	1L squamous in combination with platinum/taxane
	3f[e]	3L+, ALK-translocation/ROS1 rearrangement positive
	3g[e]	3L+, EGFR mutation/deletion
	3h[f]	2L, following platinum-based doublet cytotoxic chemotherapy combined with anti-PD-1
	3i	Patients enrolled under an earlier protocol version who are no longer eligible for Cohorts 3a.1 to 3h
Urothelial	4a[d]	1L, cisplatin ineligible
	4a[d,g]	1L, refused standard of care
	4b[c]	2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory
	4c	Patients enrolled under an earlier protocol version who are no longer eligible for Cohorts 4a and 4b
TNBC	5a[b]	1-2L, I-O therapy naive
	5b[c]	1-2L, I-O therapy naive in combination with nab-paclitaxel
	5c[c]	1-2L, I-O therapy naive in combination with eribulin
	5d	Patients enrolled under an earlier protocol version who are no longer eligible for Cohorts 5a to 5c
HR+ HER2- BC	6a[c]	I-O therapy naive following hormonal therapy
	6b[c]	I-O therapy naive following hormonal and cytotoxic therapy
Gastric	7[d]	2-3L, I-O therapy naïve
CRC	8a[c]	2-3L, I-O therapy naive; MSI-high
	8b[c]	3-4L, I-O therapy naive; MSI-non-high
SCLC	9[e]	2L, I-O therapy naive

Abbreviations: CRC = colorectal carcinoma; 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 closed under Amendment 5.1.
c. Cohorts closed with an administrative letter dated 29 March 2019.
d. Cohorts closed under Amendment 6.
e. Cohorts never opened for screening.
f. Cohorts closed with an administrative letter dated 22 January 2020.

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

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)
The safety and tolerability of NKTR-214 in combination with nivolumab and ipilimumab will be evaluated in approximately 36 1L patients with advanced or metastatic RCC, NSCLC, melanoma, or urothelial carcinoma.

Cohort A (concurrent dosing) is the first schedule to be evaluated with administration of all 3 study drugs on the same day (NKTR-214/nivolumab/ipilimumab) (see first table below). The Cohort A maintenance dose will be administered continuously after the last dose of ipilimumab for dosing schedules 2 and 3. The first patient in each of the 3 dosing schedules listed (see second table below) will be enrolled and assessed for 7 days prior to the enrollment of patients 2 to 6 in each dosing schedule. Based on emerging safety and biomarker data from Cohort A, Cohort B may be explored for the following scenarios:

- For each of the 3 dosing schedules, unless the safety profile of the triplet combination is deemed unacceptable by the sponsor and investigators.
- If available biomarker data from the patients in Cohort A indicate sub-optimal T cell activation with concurrent dosing.

For either Cohort A or B, the dose levels of NKTR-214 for a given dosing schedule may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested. The DLT evaluation period for the NKTR-214/nivolumab/ipilimumab triplet therapy will begin with the first dose of ipilimumab and the evaluation period will be a minimum of 3 weeks (21 days). DLT evaluation will be based on the study dose schedule as detailed in Section 5.11.

Part 3 is closed to patient screening and enrollment under Amendment 7.

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

Cohort	C1D1	C2D1	C3D1	C4D1	C5D1[a]
A (Concurrent)	NKTR-214 nivolumab ipilimumab	NKTR-214 nivolumab	NKTR-214 nivolumab ipilimumab	NKTR-214 nivolumab	NKTR-214 nivolumab ipilimumab[b]
B (Staggered)	NKTR-214 nivolumab	NKTR-214 nivolumab	NKTR-214 nivolumab ipilimumab	NKTR-214 nivolumab	NKTR-214 nivolumab ipilimumab[b]

Abbreviations: C1D1 = Cycle 1 Day 1; C2D1 = Cycle 2 Day 1; C3D1 = Cycle 3 Day 1, etc
a Only the first 5 cycles are shown
b Ipilimumab will be continuously dosed q6w (as shown in table below) or q3w only for 4 doses based on assigned dosing schedule

Part 3 Cohort A: Concurrent Dosing Schedules

Dosing Schedule	Indication	N[a]	NKTR-214 q3w	Nivolumab q3w	Ipilimumab q3w or q6w	Maintenance Dose[b] q3w
1	RCC[c] NSCLC[d]	12	0.006 mg/kg	360 mg flat dose	1 mg/kg q6w	n/a
2	Urothelial[d]	12	0.006 mg/kg			

	Melanoma[d]			1 mg/kg × 4 doses	3 mg/kg q3w × 4 doses	NKTR-214 0.006 mg/kg + nivolumab 360 mg
3	RCC[d]	12	0.006 mg/kg	3 mg/kg × 4 doses	1 mg/kg q3w × 4 doses	
	Melanoma[d]					

a Enrollment will be up to 12 patients.
b NKTR-214 at 0.006 mg/kg and nivolumab at 360 mg will be dosed continuously q3w after the last dose of ipilimumab for dosing schedules 2 and 3 following the 4 doses of nivolumab and ipilimumab and NKTR-214.
c This cohort is a historical cohort and was closed to patient enrollment under Amendment 6.
d Cohorts closed with an administrative letter dated 22 January 2020.

The Safety Review Committee will jointly decide the following:

- Dose and schedule for the next cohort
- RP2D
- Dose levels of NKTR-214, for a given dosing schedule, may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested.
- Decision for a recommended phase 2 dose schedule will be determined by both safety and pharmacological parameters.
- Decision to evaluate the triplet in additional patients at lower doses and/or different dose schedules within the anticipated 36 patients to better assess the benefit/risk profile.

The Sponsor may choose to concurrently enroll patients at lower dose levels and/or different dose schedules to assess the benefit/risk profile within the anticipated 36 patients. In Part 3, the RP2Ds will be established for each of the 3 dosing schedules (it may be necessary for a separate RP2D be established for patients with melanoma and urothelial cancers, if the tolerability is different between these 2 groups). When an RP2D is established in Part 3, enrollment for that dosing schedule will begin in Part 4. The sponsor will decide which dosing schedules will be opened in Part 4.

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

Enrollment into the dose expansion cohorts will commence once the RP2D for the triplet has been established in Part 3 for each respective tumor type. The maximum of patients in each cohort is listed in Section 9.2 Table 25 (based on a Historical and Target ORR); the total will include any patients from each of the 6 cohorts in Part 3, thus approximately 106 additional patients may be enrolled into Part 4 (below).

Patients will be enrolled simultaneously to each indication; for patients with melanoma, enrollment will occur simultaneously with dose schedule assigned alternately based on date of screening until one of the respective dosing schedule's enrollment is fulfilled.

Part 4 is closed to patient screening and enrollment under Amendment 7.

Part 4 Indications and Dosing Schedules

Indication	Cohort	Concurrent Dosing Schedule[a]
RCC	10a.1[b]	1
	10a.3[d]	3
NSCLC	11a.1[d]	1
Melanoma	12a.2[d]	2
	12a.3[c]	3
Urothelial	13a.2[d]	2

	a If staggered dosing is to be tested, matching cohorts will be named as follows: the letter 'a' will be substituted with 'b' (e.g., for the urothelial indication, concurrent dosing Cohort 13a.2 will be named staggered dosing Cohort 13b.2). b This cohort is a historical cohort for both concurrent and staggered dosing and was closed to enrollment under Amendment 6. c This cohort was closed with an administrative letter dated 29 March 2019. d Cohorts closed with an administrative letter dated 22 January 2020. 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).
Key Eligibility Criteria:	Under Amendment 7, the study is closed to patient screening and enrollment. 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** Under Amendment 7, the study is closed to patient screening and enrollment. • 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)** Under Amendment 7, the study is closed to patient screening and enrollment. **For Disease-Specific Tumor Types** **<u>Melanoma</u>** • Histologically confirmed stage III (unresectable) or stage IV melanoma, as per American Joint Committee on Cancer (AJCC) staging system. • Patients must consent to BRAF testing or have documented BRAF status as per regionally acceptable V600 mutational status testing. • Uveal melanoma will be excluded. • "Isolated limb perfusion" is not considered systemic chemotherapy.

	Cohort 1a − Melanoma (1L) • Have not received prior anti-cancer therapy for advanced or metastatic melanoma. For Part 2: • 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. • Patients must not have received any prior therapy for melanoma (including therapy for neoadjuvant, adjuvant, locally advanced or metastatic disease, including all systemic therapy including tyrosine kinase inhibitors [BRAF, MEK, mTOR], bevacizumab, I-O therapy, cytotoxic chemotherapy, and/or isolated limb perfusion). **Cohort 1b − Melanoma (2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory)** • Patients must have received only 1 prior line of therapy with an anti-PD-1 or anti-PD-L1 containing regimen (doublet-based therapy), which must be their most recent anti-cancer treatment. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens. • Patients must have confirmed radiographic or biopsy-proven disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 containing regimen. Patients must consent to providing pre-study scans (if available) to confirm radiographic progression. • Patients may have received only 1 prior line of therapy with molecular-targeted therapy. • Patients who have received only 1 prior regimen of cytotoxic chemotherapy, but have not received prior molecular targeted therapy, are eligible. • Patients may not have primary refractory disease to prior anti-PD-1 therapy (radiographic or clinical progression within 120 days of initiation of immuno-oncology therapy). **Cohort 1c – Melanoma BRAF wild type (2L, anti-PD-1 or anti-PD-L1 relapse/refractory)** • Patients must be BRAF wild type. • Patients must have received only 1 prior line of therapy with single-agent anti-PD-1 or anti-PD-L1 therapy, which must be their most recent anti-cancer treatment. Patients must not have received anti-CTLA-4 alone or in combination with anti-PD-1 or anti-PD-L1. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens. • Patients are not eligible who received adjuvant or first-line therapy for advanced/metastatic disease consisting of molecular target therapies including, but not limited to, BRAF, MEK, or C-KIT targeted therapies (single agent or in any combination), or intralesional therapy. • Patients are not eligible who received doublet immuno-oncology therapy, including checkpoint inhibitors combined with either systemic or intralesional therapy. Patients are not eligible who received cytotoxic chemotherapy such as dacarbazine, paclitaxel or others.

	• Patients must have confirmed radiographic or biopsy-proven disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 therapy. • Patients must consent to providing pre-study scans (if available) to confirm radiographic progression. **Cohort 1d – Melanoma (1L following prior adjuvant therapy)** • Have not received prior anti-cancer therapy for advanced or metastatic melanoma • Patient must have received prior adjuvant therapy for melanoma; adjuvant therapy may consist of any immuno-oncology regimens (single-agent or combination therapy) or molecularly targeted therapy(such as tyrosine kinase inhibitors). The disease-free interval from last dose of adjuvant therapy to a diagnosis of advanced or metastatic melanoma must be less than 180 days. **Cohort 1e − Melanoma** • Patients who were enrolled under an earlier version of the protocol who are no longer eligible for Cohorts 1a through 1d. **<u>Renal Cell Carcinoma (RCC)</u>** • 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. **Cohort 2b − RCC (2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory)** • Patients must have received only 1 prior line of therapy with an anti-PD-1 or anti-PD-L1 containing regimen, which must be their most recent anti-cancer treatment. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens. • Patients must have confirmed radiographic disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 containing regimen. Patients must consent to providing pre-study scans (if available) to confirm radiographic progression. **Cohort 2c – Renal Cell Carcinoma** • Patients who were enrolled under an earlier version of the protocol who are no longer eligible for Cohorts 2a or 2b. **<u>Non-Small Cell Lung Cancer (NSCLC)</u>** • Histologically confirmed or cytologically confirmed diagnosis of stage IV NSCLC (unless otherwise noted)

	• Patients with nonsquamous NSCLC must lack both epidermal growth factor receptor (EGFR)-sensitizing mutation/deletion and anaplastic lymphoma kinase (ALK) translocation by local testing (assessment of ROS1 mutation status is not required, unless otherwise noted). For ALK or EGFR testing, an FDA-approved test or validated assay should be used as applicable for selection of patients. For patients with squamous NSCLC, testing for EGFR, ALK, or ROS1 is not required. **Cohorts 3a.1, 3a.2, 3a.3, and 3a.4 − NSCLC (1L)** • Patients must have known PD-L1 status as per validated immunohistochemistry testing. Up to 20 efficacy-evaluable patients will be enrolled in each subgroup of PD-L1 negative (PD-L1 < 1%; Cohort 3a.1), PD-L1 highly positive (PD-L1 ≥ 50%; Cohort 3a.3), or PD-L1 low/intermediate (PD-L1 ≥ 1% - < 50%; Cohort 3a.2). For patients who do not have known PD-L1 status, testing must be done using an FDA-approved PD-L1 test. An abbreviated consent may be presented to the patient prior to the Screening period to permit early assessment of the PD-L1 status of the tissue sample. Patients enrolled in Cohort 3a who do not have a PD-L1 status assessed by central testing will be assigned to Cohort 3a.4. • Patients must not have received prior anti-cancer therapy for advanced or metastatic NSCLC; patients must not have received prior immuno-oncology in any setting (including neoadjuvant, adjuvant, locally advanced or metastatic disease). **Cohort 3b − NSCLC (2L, I-O therapy naive) following platinum-based therapy** • Patients must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease. Patients are not eligible who refused prior platinum-based therapy. • Patients who received platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible. • Patients must not have received any prior immuno-oncology in any setting 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. **Cohort 3c − NSCLC (2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory)** • Patients must have received only 1 prior line of therapy with anti-PD-1 or anti-PD-L1 therapy. Patients are eligible if they received sequential therapy (e.g., cytotoxic chemotherapy followed by anti PD-1 or anti PD-L1 therapy, or vice versa). Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens. • Patients must not have received anti-CTLA-4 alone or in combination with anti-PD-1 or anti-PD-L1, unless the anti-CTLA-4 therapy stopped > 1 year prior to Cycle 1 Day 1. • Prior to the anti-PD-1 or anti-PD-L1 therapy regimen, patients must have received zero or 1 prior line of cytotoxic chemotherapy for metastatic disease. • Patients must have confirmed radiographic disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 containing regimen.

	Patients must consent to providing pre study scans (if available) to confirm radiographic progression. • Patients may not have primary immuno-oncology refractory disease (radiographic or clinical progression within 120 days of initiation of immuno-oncology therapy). **Cohorts 3d.1 and 3d.2 − NSCLC (1L nonsquamous) (in combination with platinum/pemetrexed and maintenance pemetrexed [Cohort 3d.1] or without maintenance pemetrexed [Cohort 3d.2])** • Patients must have nonsquamous NSCLC. The patient will be excluded if the histology is considered predominantly squamous cell NSCLC. Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the patient is ineligible. • Patients must not have received prior anti-cancer therapy for advanced or metastatic NSCLC; patients who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the development of metastatic disease. Patients must not have received prior immuno-oncology therapy in any setting (including neoadjuvant, adjuvant, locally advanced or metastatic disease). • Patients must be candidates for platinum/pemetrexed chemotherapy and willing to take folic acid and vitamin B12 supplementation. • Patients must not have received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of study medication. **Cohort 3e − NSCLC (1L squamous) (in combination with platinum/taxane)** • Patients must have squamous NSCLC. • Patients must not have received prior anti-cancer therapy for advanced or metastatic NSCLC; patients who received adjuvant or neoadjuvant chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy are eligible. Patients must not have received prior immuno-oncology therapy in any setting (including neoadjuvant, adjuvant, locally advanced or metastatic disease). • Patients must be candidates for platinum/taxane chemotherapy. • Patients must not have received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of study medication. • Known hypersensitivity to the selected cytotoxic chemotherapy study drugs. **Cohort 3f − NSCLC (3L+, ALK-translocation/ROS1 rearrangement positive)** • Patients must have ALK-translocation positive or ROS1 rearrangement NSCLC by local pathology report (assessment of ROS1 mutation status is not required). For ALK testing, an FDA-approved test or validated assay must be used. • Patients must have received at least two prior anti-cancer therapies for advanced or metastatic NSCLC (these may have included chemotherapy and must have included at least one ALK-directed and/or ROS-1-directed therapy), be ineligible to receive these therapies due to toxicity, or no longer be considered a candidate for additional tyrosine kinase inhibitor therapy; patients must not have received prior immuno-oncology therapy in any setting (including neoadjuvant, adjuvant, locally advanced or metastatic disease). • Patients may not have received more than one prior cytotoxic-based regimen (e.g., carboplatin with paclitaxel). **Cohort 3g − NSCLC (3L+, EGFR mutation/deletion)** • Patients must have EGFR mutation or relevant deletion NSCLC by local pathology report. For EGFR testing, an FDA-approved test or validated assay should be used.

	• Patients must have received at least two prior anti-cancer therapies for advanced or metastatic NSCLC (these may have included chemotherapy and must have included at least one EGFR-directed small molecule therapy), be ineligible to receive these therapies due to toxicity or no longer be considered a candidate for additional tyrosine kinase inhibitor therapy; patients must not have received prior I-O therapy in any setting (including neoadjuvant, adjuvant, locally advanced or metastatic disease). • Patients may not have received more than one prior cytotoxic-based regimen (e.g., carboplatin with paclitaxel). **Cohort 3h − NSCLC (2L, anti PD 1 or anti PD L1 relapse/refractory)** • Patients must have received only 1 prior line of therapy with anti PD-1 or anti PD-L1 therapy in combination with doublet platinum-containing cytotoxic chemotherapy, which must be their most recent anti-cancer treatment. Patients are not eligible if they received sequential therapy (e.g., cytotoxic chemotherapy doublet therapy followed by anti PD-1 or anti PD-L1 therapy or vice versa). Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens. • Patients must not have received more than 1 prior line of cytotoxic chemotherapy for metastatic disease. • Patients must have confirmed radiographic disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 containing regimen. Patients must consent to providing pre study scans (if available) to confirm radiographic progression. • Patients may not have primary immuno-oncology refractory disease (radiographic or clinical progression within 120 days of initiation of immuno-oncology therapy). **Cohort 3i – NSCLC** • Patients who were enrolled under an earlier version of the protocol who are no longer eligible for Cohorts 3a.1 to 3h. **<u>Urothelial Carcinoma</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. **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. **Cohort 4b – Urothelial Carcinoma (2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory)** • Patients must have progressed on only one prior line of therapy that contains platinum-based chemotherapy in the metastatic setting or post platinum-based chemotherapy in an adjuvant setting with progression < 6 months. • Patients must have received only one prior line of therapy with single-agent anti-PD-1 or anti-PD-L1 therapy, which must be their most recent anti-cancer treatment. Patients must not have received anti-CTLA-4 alone or in combination with anti-PD-1 or anti-PD-L1. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens. • Patients must have confirmed radiographic disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 therapy. Patients must consent to providing pre-study scans (if available) to confirm radiographic progression. Patients may not have primary immuno-oncology refractory disease (radiographic or clinical progression within 120 days of initiation of immuno-oncology therapy). **Cohort 4c − Urothelial** • Patients who were enrolled under an earlier version of the protocol who are no longer eligible for Cohorts 4a or 4b. **Cohort 5 − <u>Triple-Negative Breast Cancer (1-2L, I-O therapy naive)</u>** • Patients must have diagnosis of advanced triple-negative breast cancer (TNBC) (“advanced” is defined either locally advanced breast cancer not amenable to curative surgery or radiotherapy or distant metastases). • Less than 1% of tumor cell nuclei test positive for estrogen and progesterone receptors determined by using standard immunohistochemistry (IHC). • Human epidermal growth factor receptor 2 (HER2) negative as determined by local pathologist, using IHC or in situ hybridization. • Patients must have had triple negative phenotype of breast cancer in all available biopsies that have been examined during the course of the disease. • Patients must have received 0 or 1 prior line of therapy with systemic cytotoxic chemotherapy for advanced TNBC or patient refuses standard of care. Substitution within a class of anti-cancer therapy (e.g., nab-paclitaxel for paclitaxel; carboplatin for cisplatin) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received 1 prior line of therapy. • Patients are excluded whose disease-free interval (for patients with prior neoadjuvant or adjuvant chemotherapy: the interval between the last dose of neoadjuvant or adjuvant chemotherapy to the diagnosis of advanced breast cancer; for patients originally diagnosed with Stage I/II/III breast cancer who did not receive prior neoadjuvant or adjuvant chemotherapy: the interval between date of original diagnosis of breast cancer and date of diagnosis of advanced breast cancer) is less than 6 months and no clinically significant tumor-related symptoms

	in the judgment of the investigator. Patients with a diagnosis of de novo Stage IV breast are eligible. • Patients are excluded if the screening LDH > 2 × ULN (based on the central laboratory). • Must not have received any prior 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-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. **Cohort 5a – <u>Triple-Negative Breast Cancer (1-2L, I-O therapy naive)</u>** • Patients must be a candidate for NKTR-214 in combination with nivolumab. **Cohort 5b – <u>Triple-Negative Breast Cancer (1-2L, I-O therapy naive)</u> in combination with nab-paclitaxel** • Patients must be a candidate for single-agent nab-paclitaxel; patients may not have received paclitaxel or docetaxel for metastatic carcinoma and may not have relapsed with metastatic disease within 1 year of adjuvant paclitaxel or docetaxel treatment. • Patients may not have received prior nab-paclitaxel in any setting. **Cohort 5c – <u>Triple-Negative Breast Cancer (1-2L, I-O therapy naive)</u> in combination with eribulin** • Patients must be a candidate for single-agent eribulin; patients may not have relapsed with metastatic disease within 1 year of adjuvant taxane-based treatment. • Patients may not have received prior eribulin in any setting. **Cohort 6 − Hormone-Receptor Positive, HER2 Negative Breast Cancer** • Patients must have diagnosis of advanced hormone-receptor positive breast carcinoma (“advanced” is defined either locally advanced breast cancer not amenable to curative surgery or radiotherapy or metastatic disease). • ≥ 1% of tumor cell nuclei test positive for estrogen or progesterone receptors determined by using standard IHC • HER2 negative as determined by local pathologist, using IHC or in situ hybridization • For patients whose primary tumor was HER2-positive or hormone-receptor positive, eligibility will be based on the first biopsy for advanced disease. • Patients must have either archival or fresh tumor biopsy that demonstrates ≥ 1% positive PD-L1 staining by the central pathology laboratory. An abbreviated consent may be presented to the patient prior to the Screening period to permit early assessment of the PD-L1 status of the tissue sample. • Patients must have received prior aromatase and fulvestrant therapy for advanced breast cancer. (Progression after prior adjuvant therapy with an aromatase inhibitor within 12 months will count as a line of therapy). Hormonal therapy may have been administered as single-agent or in combination with CDK4-6 inhibitors (such as palbociclib and others), mTOR inhibitors (everolimus and others), PI3K inhibitors (buparlisib and others), or other agents used in combination with hormonal agents (AKT inhibitors, WNT inhibitors, or others). • Must not have received any prior 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-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. **Cohort 6a – Hormone-Receptor Positive, HER2-Negative Breast Cancer (I-O therapy naive following hormonal therapy)** • Patients must not have received prior cytotoxic chemotherapy (such as tubulin-targeting agents (paclitaxel, docetaxel, nab-paclitaxel, eribulin, vinca alkaloids, epothilones, and others), anti-metabolites (5-fluorouracil, capecitabine, gemcitabine, and others), platinum agents (carboplatin, cisplatin, and others), alkylating agents (cyclophosphamide and others), topoisomerase 1 or 2 inhibitors (irinotecan, doxorubicin, epirubicin, etoposide, and others) or VEGF-targeted monoclonal antibodies (bevacizumab and others). Prior systemic therapy must be reviewed by the Medical Monitor prior to registration for the trial. **Cohort 6b – Hormone-Receptor Positive, HER2-Negative Breast Cancer (I-O therapy naive following hormonal and cytotoxic therapy)** • Patients must have received at least one and up to 2 prior lines of cytotoxic chemotherapy (such as tubulin-targeting agents (paclitaxel, docetaxel, nab-paclitaxel, eribulin, vinca alkaloids, epothilones, and others), anti-metabolites (5-fluorouracil, capecitabine, gemcitabine, and others), platinum agents (carboplatin, cisplatin, and others), alkylating agents (cyclophosphamide and others), topoisomerase 1 or 2 inhibitors (irinotecan, doxorubicin, epirubicin, etoposide, and others). Substitution within a class of anti-cancer therapy (e.g., carboplatin for cisplatin) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received a prior line of therapy. Prior systemic therapy must be reviewed by the Medical Monitor prior to registration for the trial. **Cohort 7 − Gastric Carcinoma (2-3L, I-O therapy naive)** • Patients must have diagnosis of advanced gastric adenocarcinoma or gastroesophageal carcinoma (GC) ("advanced" is defined either locally recurrent surgically unresectable advanced cancer or metastatic disease). • Patients must have either archival or fresh tumor biopsy that demonstrates PD-L1 staining (Combined Positive Score ≥ 1 as determined by an FDA-approved test or validated assay). An abbreviated consent may be presented to the patient prior to the Screening period to permit early assessment of the PD-L1 status of the tissue sample. • Patients must have received no more than two prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy, and (if appropriate) HER2-targeted systemic therapy for gastric cancer. These drugs may have been administered in the neoadjuvant, adjuvant, locally advanced or metastatic setting. Patients may have progressed or been intolerant to these therapies. ("Systemic therapy" includes all agents, including cytotoxic, molecularly targeted or other). Substitution within a class of anti-cancer therapy (e.g., capecitabine for fluorouracil [5-FU]; carboplatin for cisplatin) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received a prior line of therapy. • Must not have received any prior 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-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.

	Cohort 8a − Colorectal Carcinoma (2-3L, I-O therapy naive); microsatellite instability (MSI)-high • Patients must have diagnosis of advanced colorectal carcinoma (CRC) ("advanced" is defined either locally advanced unresectable cancer or metastatic disease). • Patients must have either archival or fresh tumor biopsy that demonstrates microsatellite instability high or mismatch repair deficient disease. An abbreviated consent may be presented to the patient prior to the Screening period to permit early assessment of the CD8+ TIL status of the tissue sample. • Patients who had disease progression during, after, or were intolerant to, prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy (patients must have received either fluoropyrimidine and oxaliplatin-containing chemotherapy OR fluoropyrimidine and irinotecan-containing chemotherapy for colorectal carcinoma ("FOLFOX" [fluorouracil, leucovorin, and oxaliplatin] or "FOLFIRI" [5-fluorouracil, leucovorin, and irinotecan]); and (if appropriate) EGFR-targeted and/or VEGF-targeted systemic therapy. These drugs may have been administered in the neoadjuvant, adjuvant, locally advanced or metastatic setting. ("Systemic therapy" includes all agents, including cytotoxic, molecularly targeted or other). Substitution within a class of anti-cancer therapy (e.g., capecitabine for 5-FU) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received a prior line of therapy. • Must not have received any prior 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-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. **Cohort 8b − Colorectal Carcinoma (3-4L, I-O therapy naive); MSI-non-high** • Patients must have diagnosis of advanced colorectal carcinoma (CRC) ("advanced" is defined either locally advanced unresectable cancer or metastatic disease). • Patients must have either archival or fresh tumor biopsy that demonstrates MSI not high (MSI-stable or MSI-low) or mismatch repair proficient (pMMR) disease. In addition, tumor tissue must demonstrate CD8+ tumor infiltrating lymphocytes (≥ 10% by IHC) by central laboratory. An abbreviated consent may be presented to the patient prior to the Screening period to permit early assessment of the CD8+ TIL status of the tissue sample. • Patients must have received at least two but no more than 3 prior lines of therapy including fluoropyrimidine-, oxaliplatin and irinotecan-containing chemotherapy colorectal cancer; and (if appropriate) EGFR-targeted and/or VEGF-targeted systemic therapy. These drugs may have been administered in the neoadjuvant, adjuvant, locally advanced or metastatic setting. ("Systemic therapy" includes all agents, including cytotoxic, molecularly targeted or other). Substitution within a class of anti-cancer therapy (e.g., capecitabine for 5-FU) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received a prior line of therapy. • Must not have received any prior 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-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. **Cohort 9 − Small Cell Lung Cancer (2L, I-O therapy naive)** • Patients must have diagnosis of limited-stage or extensive-stage SCLC. • Patients must have received no more than 1 prior line of platinum-based therapy. Substitution within a class of anti-cancer therapy (e.g., carboplatin for cisplatin) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received a prior line of therapy. • Must not have received any prior 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-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. **For Parts 3 and 4 (NKTR-214/nivolumab/ipilimumab)** Parts 3 and 4 are closed to patient screening and enrollment under Amendment 7. **For Disease-Specific Tumor Types** **Cohorts 10a.1 and 10a.3 − <u>Renal Cell Carcinoma (1L), as follows:</u>** **Cohort 10a.1 concurrent dosing schedule 1 (this cohort was closed to enrollment under Amendment 6.0)** **Cohort 10a.3 concurrent dosing schedule 3** • Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC stage IV) RCC. • Histologically confirmed RCC with a clear-cell component. • Patients must not have 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. **Cohort 11a.1 − <u>Non-Small Cell Lung Cancer (1L)</u>** • Histologically confirmed or cytologically confirmed diagnosis of stage IV NSCLC • Patients with nonsquamous NSCLC must lack both EGFR-sensitizing mutation/deletion and anaplastic lymphoma kinase (ALK) translocation by local testing (assessment of ROS1 mutation status is not required). For ALK or EGFR testing, an FDA-approved test or validated assay should be used as applicable for selection of patients. For patients with squamous NSCLC, testing for EGFR and ALK is not required. • Patients must not have received prior anti-cancer therapy for advanced or metastatic NSCLC. • Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

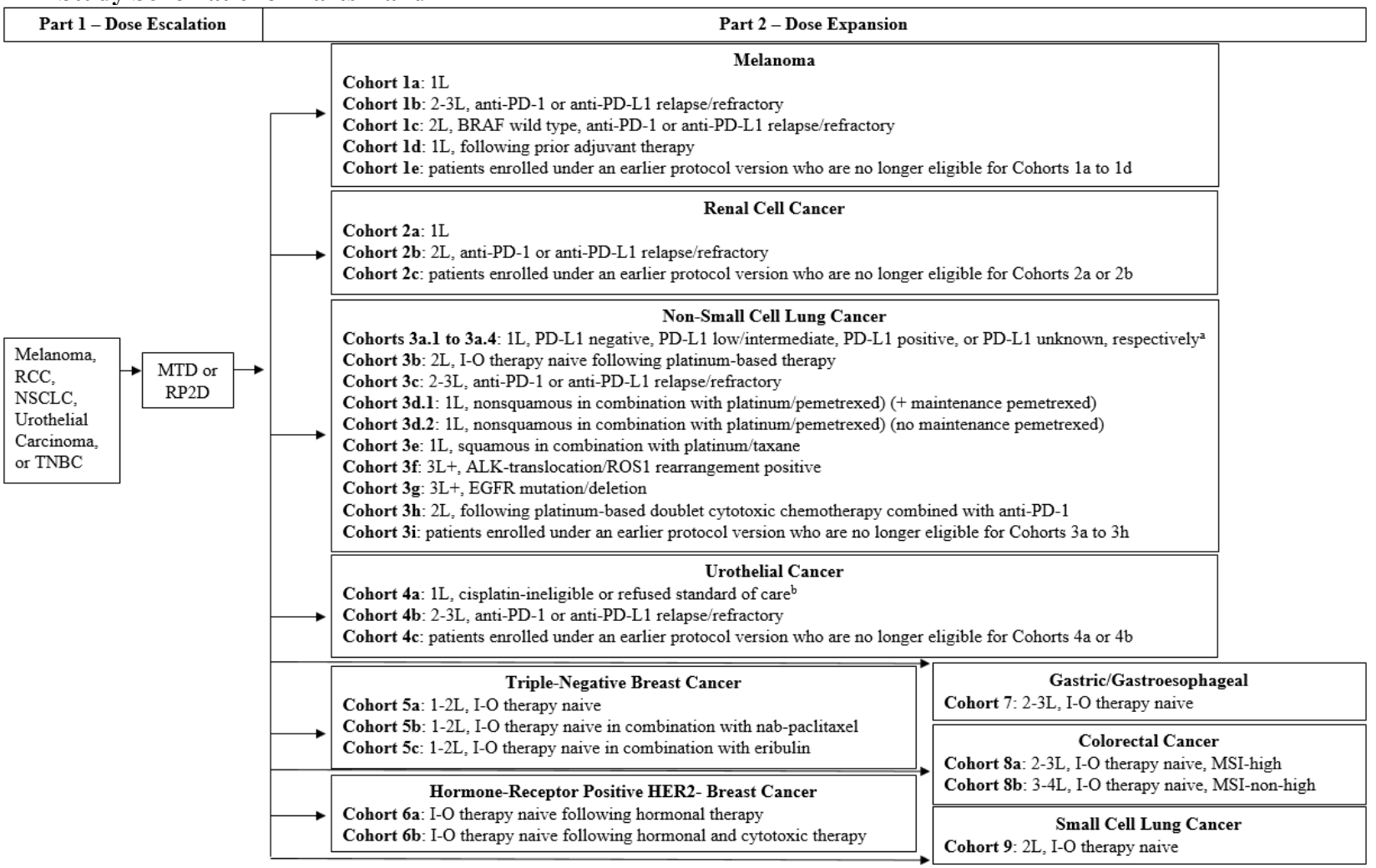
	Cohorts 12a.2 and 12a.3 − <u>Melanoma (1L), as follows:</u> • **Cohort 12a.2: concurrent dosing schedule 2** • **Cohort 12a.3: concurrent dosing schedule 3** • Histologically confirmed stage III (unresectable) or stage IV melanoma, as per American Joint Committee on Cancer (AJCC) staging system. • Patients must consent to BRAF testing or have documented BRAF status as per regionally acceptable V600 mutational status testing. • Uveal melanoma will be excluded. • Have not received prior anti-cancer therapy for advanced or metastatic melanoma. • 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. • Prior to disease metastasis, patients must not have received neoadjuvant or adjuvant tyrosine kinase (BRAF, MEK, mTOR), bevacizumab or intralesional therapy. **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 (Parts 2, 3, and 4) Nivolumab (anti-PD-1) administered IV over 30 (± 5) minutes at either a 360 mg flat dose q3w (Parts 2, 3, and 4), 1 mg/kg q3w × 4 doses or 3 mg/kg q3w × 4 doses (Parts 3 and 4)

	Ipilimumab administered IV over 30 (± 5) minutes at 1 mg/kg q6w, 3 mg/kg q3w × 4 doses or 1 mg/kg q3w × 4 doses (Parts 3 and 4) Part 2 Institutional guidelines for administration of other anti-cancer therapies should be followed in Part 2. • Cohort 3d.1 NSCLC (1L nonsquamous): NKTR-214 followed by nivolumab (q3w) followed by investigator's choice of cisplatin 75 mg/m^2 administered IV or carboplatin AUC 5 followed by pemetrexed 500 mg/m^2 q3w by IV administration for 4 cycles followed by maintenance NKTR-214, nivolumab, and pemetrexed q3w • Cohort 3d.2 NSCLC (1L nonsquamous): NKTR-214 followed by nivolumab (q3w) followed by investigator's choice of cisplatin 75 mg/m^2 administered IV or carboplatin AUC 5 followed by pemetrexed 500 mg/m^2 q3w by IV administration for 4 cycles followed by maintenance NKTR-214 and nivolumab q3w • Cohort 3e NSCLC (1L squamous): NKTR-214 followed by nivolumab (q3w) followed by either Cremophor-based paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle or nab-paclitaxel 100 mg/m^2 by IV administration on Days 1, 8, and 15 of each 21-day cycle with investigator's choice of either carboplatin AUC 6 by IV administration on cycle Day 1 q3w for 4 cycles or cisplatin 75 mg/m^2 q3w by IV administration for 4 cycles followed by maintenance NKTR-214 and nivolumab q3w. • Cohort 5b TNBC (1-2L): NKTR-214 followed by nivolumab (q3w) followed by nab-paclitaxel 260 mg/m^2 by IV administration q3w. • Cohort 5c TNBC (1-2L): NKTR-214 followed by nivolumab (q3w) followed by eribulin mesylate 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2) by IV administration on Days 1 and 8 q3w.
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 objective response rate (ORR) (defined as the number of patients with a best overall response of complete response or partial response divided by the number of response evaluable 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)
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 using the response evaluable population. ORR will also be summarized for the intent-to-treat (ITT) population based on an independent radiology review. The BOR will be summarized similarly. The TTR will be summarized by descriptive statistics. The DOR will be summarized using the Kaplan-Meier method for patients with CR or PR as BOR. The OS and PFS will be summarized by the Kaplan-Meier method using the ITT population. Efficacy assessments based on irRECIST will be evaluated. **Pharmacokinetics and Pharmacodynamics:** Pharmacokinetic parameters will be tabulated and summarized with descriptive statistics. [redacted]

1.1 Study Schematics

Figure 1: Study Schematic for Parts 1 and 2

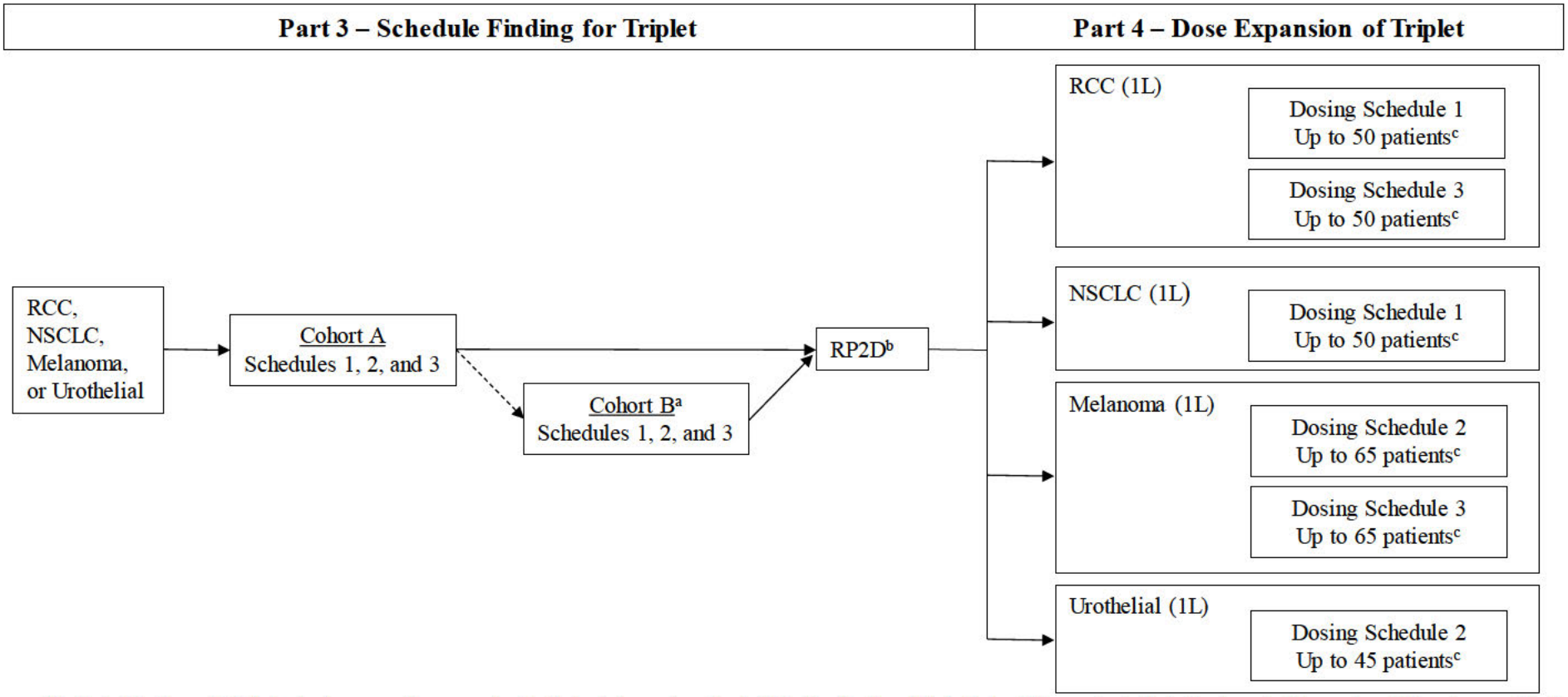


Abbreviations: HR+ = hormone-receptor positive; I-O = immuno-oncology; L = line; MSI = microsatellite instability; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; RP2D = recommended Phase 2 dose; SOC = standard of care; TNBC = triple-negative breast cancer

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

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

Figure 2: Study Schematic for Parts 3 and 4



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

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

c. Includes patients from both Part 3 and Part 4

1.2 Schedule of Events

Table 1: Schedule of Events for Part 1

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**	**End of Treatment[u]**	**Follow up 3 mo[t]**
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		X	X	X				
ECHO/MUGA	X[e]										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	Refer to Section 5.10.2										

Table 1: Schedule of Events for Part 1 (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**	**End of Treatment[u]**	**Follow up 3 mo[t]**
Immunogenicity serum sample[m]		X							X[m]		X	X[m]
Tumor assessment[n]	X								Every 8 weeks (± 7d)			X
[redacted]		[redacted]					[redacted]		[redacted]	[redacted]		
NKTR-214 PK blood sample[q]		X	X	X	X	X	X	X	X	X		
Nivolumab PK blood sample[q]		X							X[q]			
Administer IV fluids[r]		X							X			
Drug administration[s]		X							X			
Long-term follow-up[t]												X

Footnotes:

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

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 7.15.

c. Some clinic visits will have more frequent vital sign measurements. See Sections 5.3.7.1 and 7.16.

d. In Cycle 1 only, ECGs are performed prior to each NKTR-214 PK sampling time. 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. See Section 7.18.

f. See Section 7.19.

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 (FFPE), archival tumor tissue sections on slides are acceptable, see Section 5.10.2 for additional details.

l. Unstained FFPE, tumor tissue sections on slides (a minimum of 3) or FFPE tumor tissue blocks from a recent biopsy, collected within 12 months prior to Cycle 1 Day 1 and without intervening therapy, are acceptable in lieu of a fresh tumor biopsy prior to treatment. The biopsy sampling schedule is provided in Section 5.10.2.

m. See Section 5.9.

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.

[redacted]

p. See Section 5.10.3.

q. See Section 5.8. 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. See Section 5.3.7.2.

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

t. See Sections 5.5, 7.5, and 7.8.

u. See Sections 5.4, 7.5, and 7.8.

Table 2: Schedule of Events for Part 2

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 3**	**Day 8**	**End of Treatment[w]**	**Follow up 3 mo[v]**
Physical examination[b]	X	X			X	X			X	
Vital signs[c]	X	X[c]	X[c]	X[c]	X	X[c]		X[c]	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 [h]	X					X[h]			X	
Local labs prior to dosing [i]		X[i]				X[i]				
Urinalysis (dipstick)[j]	X	X				X			X	
Serology[h]	X									
Archival tumor tissue[k]	X									
Tumor biopsy[l]	X	Refer to Section 5.10.2								

Table 2: Schedule of Events for Part 2 (Cont'd)

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 3**	**Day 8**	**End of Treatment[w]**	**Follow up 3 mo[v]**
Immunogenicity serum sample[m]		X				X			X	X
Tumor assessment[n]	X					Every 8 weeks (± 7d)				X
[redacted]		[redacted]			[redacted]	[redacted]		[redacted]		
Stool sample collection[p]	X					X[p]				
NKTR-214 PK blood sample[q]		X		X	X	X				
Nivolumab PK blood sample[q]		X				X				
BRAF mutation testing[r]	X									
Administer IV fluids[s]		X				X				
Drug administration[t]		X				X				
Oral hydration follow-up[u]				X[v]			X[v]			
Long-term follow-up[v]										X

Footnotes:

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

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. Study assessments, including imaging, may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays after permission from the medical monitor. 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 7.15.

c. Some clinic visits will have more frequent vital sign measurements. See Appendix 2 Schedule of Assessments and Sections 5.3.7.1 and 7.16. Beginning on Day 8 of Cycle 3 and beyond, vital signs should be collected according to the Investigator's discretion based on the clinical status of the patient.

d. See Section 7.17. 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. See Section 7.18.

f. See Section 7.19.

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. See Section 5.3.7.2 and Appendix 1B.

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

k. Unstained FFPE, archival tumor tissue sections on slides are acceptable, see Section 5.10.2 for additional details.

l. The biopsy sampling schedule is provided in Section 5.10.2. Unstained FFPE, 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. 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. Section 5.10.2 provides additional tumor tissue biopsy requirements.

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.

[redacted]

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. Between 2 and 4 days following administration of the first two doses of NKTR-214 in Cycles 1 and 2, site personnel must contact the patient (by telephone or clinic visit) to remind the patient of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion (Section 5.3.7.2). In subsequent NKTR-214 administrations in Cycle 3 and beyond, the oral hydration follow-up should be conducted as clinically indicated (Section 5.3.7.2).

v. See Sections 5.5, 7.5, and 7.8.

w. See Sections 5.4, 7.5, and 7.8.

Table 3: Schedule of Events for Parts 3 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 11**	**Day 1**	**Day 3**	**Day 8**	**End of Treatment[w]**	**Follow up 3 mo[v]**
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[c]	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	X	
Serum chemistry[h]	X	X			X	X	X		X	X	
Coagulation[h]	X	X			X	X	X		X	X	
Additional labs [h]	X					X	X[h]			X	
Local labs prior to dosing [i]		X[i]					X[i]				
Urinalysis (dipstick)[j]	X	X					X			X	
Serology[h]	X										
Archival tumor tissue[k]	X										
Tumor biopsy[l]	X	Refer to Section 5.10.2									
Immunogenicity serum sample[m]		X					X			X	X
Tumor assessment[n]	X						Every 8 weeks (± 7d)				X

Table 3: Schedule of Events for Parts 3 and 4 (Cont'd)

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 11**	**Day 1**	**Day 3**	**Day 8**	**End of Treatment[w]**	**Follow up 3 mo[v]**
[redacted]		[redacted]			[redacted]		[redacted]		[redacted]		
Stool sample collection[p]	X						X				
NKTR-214 PK blood sample[q]		X		X	X		X				
Nivolumab or ipilimumab PK blood sample[q]		X					X				
BRAF mutation testing[r]	Part 3 only										
Administer IV fluids[s]		X					X				
Drug administration[t]		X					X				
Oral hydration follow-up[u]				X[v]				X[v]			X
Long-term follow-up[v]											X

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

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. Study assessments, including imaging, may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays after permission from the medical monitor. 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. Samples for hematology, chemistry, coagulation, and pregnancy are drawn at the same time points in Parts 3 and 4. Local laboratories will be used for Parts 1 and 3; a central laboratory will be used for Part 2 and Part 4.

b. See Section 7.15.

c. Some clinic visits will have more frequent vital sign measurements. See Appendix 2 Schedule of Assessments and Sections 5.3.7.1 and 7.16. Beginning on Day 8 of Cycle 3 and beyond, vital signs should be collected according to the Investigator's discretion based on the clinical status of the patient.

d. See Section 7.17. 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. See Section 7.18.

f. See Section 7.19.

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. See Section 5.3.7.2 and Appendix 1B.

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. The biopsy sampling schedule is provided in Section 5.10.2. Unstained FFPE, 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. Additional 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. Section 5.10.2 provides additional tumor tissue biopsy requirements.

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.

[redacted]

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. Between 2 and 4 days following administration of the first two doses of NKTR-214 in Cycles 1 and 2, site personnel must contact the patient (by telephone or clinic visit) to remind the patient of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion (Section 5.3.7.2). In subsequent NKTR-214 administrations in Cycle 3 and beyond, between 2 and 4 days following NKTR-214 administration, the oral hydration follow-up is mandatory for patients receiving the NKTR-214/nivolumab/ipilimumab triplet in Parts 3 or 4 following study drug administration in any cycle.

v. See Sections 5.5, 7.5, and 7.8.

w. See Sections 5.4, 7.5, and 7.8.

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 (i.e., rhIL-2 also referred to as IL-2).

Bempegaldesleukin (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-2Rβγ) 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

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 (OS), 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

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

- Withholding 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.

2.1.4.1 Observed Events of Cerebrovascular Accident in Study 16-214-02

Following the occurrence of three SAEs (one of which was fatal) of cerebrovascular accident (CVA) in the first 43 patients treated with NKTR-214, nivolumab, and ipilimumab ("triplet immunotherapy" cohort) in Study 16-214-02, a comprehensive review of CVA-related safety information for the entire clinical program for NKTR-214 (N=721) was performed. The assessment included a broad search to identify any potential CVA cases among all NKTR-214 studies; case reviews by independent neurology, cardiology, and coagulation expert consultants;

and an analysis of patient demographics, medical histories, drug exposure, laboratory values, vital signs, and PK/pharmacodynamic parameters.

Table 4 summarizes the results of the comprehensive search, which utilized a data cut-off date of 21 June 2019. A total of 3 of 43 patients (7.0%) who received triplet immunotherapy and 8 of 478 patients (1.7%) who received NKTR-214 and nivolumab ("doublet immunotherapy") in Study 16-214-02 were determined to have CVA events that were confirmed by the neurology consultants. No confirmed CVA events occurred in any patients in any other studies of NKTR-214 and nivolumab (n=115), in studies of NKTR-214 monotherapy (n=28), or in studies of NKTR-214 in combination with any other second agent (including pembrolizumab [n=12], atezolizumab [n=23], or NKTR-262 [n=22]). The incidence of CVA, combining all clinical trials in which the doublet of NKTR-214 plus nivolumab was administered was 8 out of 593 patients (1.3%).

Sections 2.1.4.1.1 and 2.1.4.1.2 summarize the CVA events observed in Study 16-214-02 for patients who received triplet immunotherapy and doublet immunotherapy, respectively, and Section 2.1.4.2 summarizes the protocol sections with additional safety measures that were implemented to mitigate the risk of CVA events and to expedite reporting of CVA events.

Table 4. CVA Adverse Events in Study 16-214-02

Regimen	Study	Patients Treated with NKTR-214 (N)	Patients with CVA[a] (n [%])
Triplet			
NKTR-214 + nivolumab + ipilimumab	16-214-02 (PIVOT-02)	43	3 (7.0)
Doublet			
NKTR-214 + nivolumab	16-214-02 (PIVOT-02)	478	8 (1.7)

a. Neurologist-confirmed CVA based on review of local magnetic resonance imaging (MRI) readings and images and other patient-related data (utilizing a data cut-off date of 21 June 2019).

2.1.4.1.1 Observed Events of Cerebrovascular Accident Following Triplet Immunotherapy

A total of 3 patients treated with triplet immunotherapy (NKTR-214 in combination with nivolumab and ipilimumab) in Study 16-214-02 were confirmed to have had a CVA by independent neurologist review.

All 3 patients (2 male, 1 female) experienced events with the preferred term of cerebrovascular accident and had the underlying malignancy of RCC. These patients had various risk factors for stroke, such as hypertension, diabetes, hyperlipidemia, and venous thrombosis. At the time of the CVA event, these patients were aged 64 years or older.

Two of the events were Grade 2 in severity and one was Grade 5. The time to onset of the events from the initial dose ranged from 33 to 222 days. All events were assessed by the investigator as related to NKTR-214, nivolumab, and ipilimumab. Two patients recovered from the CVA events; neither patient received additional NKTR-214, nivolumab, or ipilimumab on study. One patient experienced a fatal outcome.

There were 2 types of stroke patterns described in imaging of these 3 patients. The magnetic resonance imaging (MRI) of two patients included infarcts involving multiple vascular territories with border-zone appearance. The MRI of the third patient revealed a subacute infarct involving a single vascular territory in the right midbrain lateral crus cerebri.

2.1.4.1.2 Observed Events of Cerebrovascular Accident Following Doublet Immunotherapy

A total of 8 patients treated with doublet immunotherapy (NKTR-214 in combination with nivolumab) in Study 16-214-02 were confirmed to have had a CVA by independent neurologist review.

Of the 8 events that occurred in the 478 patients (1.7%) treated with the doublet immunotherapy, 4 patients experienced events with the preferred term of cerebrovascular accident, 2 with embolic stroke, one with subacute infarct, and one with encephalopathy.

The underlying malignancy was melanoma (2 patients), NSCLC (2 patients), RCC (1 patient), urothelial carcinoma (2 patients) and TNBC (1 patient). These patients had various risk factors for stroke, such as hypertension, peripheral vascular disease, hyperlipidemia, and venous thrombosis. The patients (5 male, 3 female) ranged in age from 55 to 82 years old.

All events were SAEs; none were fatal. Two were Grade 4 in severity, 4 were Grade 3, and 2 were Grade 2. The time to onset of the events from the initial dose ranged from 13 to 578 days. Four events were deemed unrelated to study drug (NKTR-214 and nivolumab) by the investigator and 4 were deemed related to study drug by the investigator (3 related to the doublet immunotherapy and 1 related to nivolumab only). These events led to discontinuation in 3 cases and dose delay in 1 case. The study treatment was continued in 1 case; 2 cases had previously discontinued both drugs. Five patients have recovered or are recovering from the CVA events, 2 of whom have recovered with sequelae (left sided paralysis in one patient and not reported in the other patient); one patient had a recurrence of the same event following rechallenge with only nivolumab and the second event was not resolved; one patient died due to progressive disease on the same day the toxicity resolved; and in 1 patient, the event was reported as “not recovered” at the time of study drug discontinuation.

Of these 8 patients:

- 6 were considered to have had an infarct involving multiple vascular territories with border-zone appearance on diffusion-weighted MRI
- 2 were considered to have had an infarct involving a single vascular territory

2.1.4.2 Mitigation Measures

Following the comprehensive review of the entire NKTR-214 clinical program, additional safety measures and analyses were implemented to mitigate the risk of CVA events and to expedite reporting of CVA events by identifying CVA as an AE of special interest (AESI). These safety measures and analyses are reflected in changes to the following protocol sections: hydration guidelines (Sections 1.2 and 5.3.7.2), CVA AE management algorithm (Appendix 3), criteria to delay, resume, or permanently discontinue study drug (Sections 5.13.1 to 5.13.3, 5.13.11, and 5.13.12, respectively), AESI (Section 7.11), and reporting AESI (Section 7.7).

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 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

Establishing that ipilimumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. Previous clinical studies of ipilimumab when administered at 3 or 10 mg/kg have used a 90-minute infusion duration; ipilimumab has been safely administered at a dose of 1 mg/kg over 30 minutes for extended treatment periods. In 120 patients treated prospectively with ipilimumab 3 mg/kg infused over 30 minutes, 7 patients (5.8%) had an infusion-related reaction; all infusion-related reactions occurred with the second dose; six were Grade 2, and one was Grade 3 (Momtaz, 2015). All 7 patients received subsequent doses of ipilimumab safely, the majority with premedication. For comparison, the 3-mg/kg dose over 90 minutes in this series (n = 457) resulted in an incidence of infusion-related reactions at 2.2%. In a second published series in which 46 melanoma patients received 100 shortened cycles of combined 3 mg/kg ipilimumab and 1 mg/kg nivolumab (each over 30 minutes), one patient (2.2%; 1 of 46 patients) had a questionable reaction after administration of 1 mg/kg nivolumab over 30 minutes (Gassenmaier, 2018). The authors concluded that the shortened infusion times for combined ipilimumab and nivolumab treatment could be safely administered. The shorter duration ipilimumab infusion is being currently investigated in larger clinical trials. Given available information comparing the 30- and 90-minute ipilimumab infusion times, ipilimumab is considered safe to infuse over 30 minutes.

2.1.9 Ipilimumab Safety Summary

The safety profile of ipilimumab was evaluated in two clinical studies in which 982 melanoma patients received ipilimumab either as monotherapy or in combination with other therapeutics.

The safety profile of ipilimumab is acceptable in the context of the observed clinical efficacy, and is manageable using established safety guidelines. The most common clinically relevant AEs typical of stimulation of the immune system were enterocolitis and hepatitis, which were manageable by delaying or stopping ipilimumab treatment and by timely immunosuppressive therapy or other supportive care.

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

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

Patients with 1L metastatic nonsquamous NSCLC were evaluated in the global, randomized, double-blind, placebo-controlled, KEYNOTE-189 study (NCT02578680), a Phase 3 study of

pemetrexed and a platinum-based drug with or without pembrolizumab, followed by pembrolizumab or placebo plus pemetrexed maintenance therapy (Gandhi, 2018).

The most common adverse event observed for the chemotherapy drugs alone (any severity regardless of causality at incidence at least 25%) included nausea, anemia, fatigue, constipation, decreased appetite, cough, and dyspnea. The most common adverse event observed for the chemotherapy drugs alone (of Grade 3 or higher severity regardless of causality at incidence at least 5%) included anemia, neutropenia, thrombocytopenia, and dyspnea. Additional details on the safety profiles of carboplatin, cisplatin, and pemetrexed are provided in the respective Package Insert or Summary of Product Characteristics.

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

A large, international, randomized Phase 3 trial compared the efficacy and safety of 100 mg/m^2 of weekly nab-paclitaxel with 200 mg/m^2 Cremophor-based paclitaxel (both combined with carboplatin targeting an area under the curve [AUC] of 6 every 3 weeks [q3w]) in 1052 patients with advanced NSCLC (Socinski, 2012).

The most common nonhematologic Grade ≥ 3 treatment-related AEs with nab-paclitaxel and Cremophor-based paclitaxel were fatigue. The most common nonhematologic grade ≥3 TRAEs with nab-paclitaxel and Cremophor-based paclitaxel were fatigue (5% and 6%, respectively), sensory neuropathy (3% and 12%), anorexia (2% and < 1%), nausea (< 1% and < 1%), myalgia (< 1% and 2%), and arthralgia (0% and 2%). The most common hematologic Grade ≥ 3 treatment-related AEs were neutropenia (47% and 58%), leukopenia (24% and 23%), thrombocytopenia (18% and 9%), and anemia (27%). Additional details on the safety profiles of carboplatin, paclitaxel, and nab-paclitaxel are provided in the respective Package Insert or Summary of Product Characteristics.

2.1.12 Safety Summary of Nab-Paclitaxel in Patients with TNBC

Patients treated in the first or second line setting for metastatic TNBC will receive nab-paclitaxel. Clinical data on nab-paclitaxel in combination with nivolumab are based on small numbers of patients (Wainberg, 2017). Data on single-agent nab-paclitaxel are therefore provided here.

In the 229 patients with metastatic breast cancer treated with single-agent nab-paclitaxel in the randomized controlled trial in patients with metastatic breast cancer, common Grade 3 to 4 hematological toxicities included neutropenia (Grade 4, 9%) with febrile neutropenia in 2%; severe anemia and thrombocytopenia were rare. Common severe non-hematological toxicities included sensory neuropathy (10%), myalgias/arthralgias (8%) and asthenia (8%). Cardiovascular toxicities included asymptomatic hypotension during the 30-minute infusion, in 5% of patients in the randomized metastatic breast cancer trial. Severe cardiovascular events possibly related to single-agent nab-paclitaxel occurred in approximately 3% of patients in the randomized trial. These events included chest pain, cardiac arrest, supraventricular tachycardia,

edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Electrocardiogram (ECG) abnormalities were reported in 60% of patients, including non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia. Most required no intervention. Alopecia was nearly universal, occurring in 90% of patients (Summary basis of approval; Gradishar, 2005).

Additional details on the safety profile of nab-paclitaxel are provided in the Package Insert or Summary of Product Characteristics.

2.1.13 Safety Summary of Eribulin in Patients with TNBC

Patients treated in the first or second line setting for metastatic TNBC will receive eribulin. Clinical data on eribulin in combination with nivolumab are in progress. Data on single-agent eribulin are therefore provided here.

Based on a large international, randomized clinical trial comparing eribulin to treatment of physician's choice conducted in 762 patients, the most common nonhematologic Grade ≥ 3 AEs included fatigue (8%), peripheral neuropathy (8%), and dyspnea (4%). The most common hematologic grade ≥ 3 AEs were neutropenia (21%) and anemia (2%). Alopecia occurred in 45% of patients (Cortes, 2011).

Additional details on the safety profile of eribulin are provided in the Package Insert or Summary of Product Characteristics.

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).

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 OS, progression-free survival (PFS), clinical benefit rate (CBR), and duration of response (DOR)

[redacted]

4.0 SELECTION OF STUDY POPULATION

Under Amendment 7, the study is closed to patient screening and enrollment.

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

Under Amendment 7, the study is closed to patient screening and enrollment.

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)

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.

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

Under Amendment 7, the study is closed to patient screening and enrollment.

For Disease-Specific Tumor Types

15. Melanoma

    a. Histologically confirmed stage III (unresectable) or stage IV melanoma, as per American Joint Committee on Cancer (AJCC) staging system.

    b. Patients must consent to BRAF testing or have documented BRAF status as per regionally acceptable V600 mutational status testing.

    c. Uveal melanoma will be excluded.

    d. "Isolated limb perfusion" is not considered systemic chemotherapy.

Cohort 1a − Melanoma (1L)

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

For Part 2:

    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.

    c. Patients must not have received any prior therapy for melanoma (including therapy for neoadjuvant, adjuvant, locally advanced or metastatic disease, including all systemic therapy including tyrosine kinase inhibitors [BRAF, MEK, mTOR], bevacizumab, I-O therapy, cytotoxic chemotherapy, and/or isolated limb perfusion).

Cohort 1b − Melanoma (2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory)

a. Patients must have received only 1 prior line of therapy with an anti-PD-1 or anti-PD-L1 containing regimen (doublet-based therapy), which must be their most recent anti-cancer treatment. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

b. Patients must have confirmed radiographic or biopsy-proven disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 containing regimen. Patients must consent to providing pre-study scans (if available) to confirm radiographic progression.

c. Patients may have received only 1 prior line of therapy with molecular-targeted therapy.

d. Patients who have received only 1 prior regimen of cytotoxic chemotherapy but have not received prior molecular targeted therapy, are eligible.

e. Patients may not have primary refractory disease to prior anti-PD-1 therapy (radiographic or clinical progression within 120 days of initiation of immuno-oncology therapy).

Cohort 1c − Melanoma BRAF wild type (2L, anti-PD-1 or anti-PD-L1 relapse/refractory)

a. Patients must be BRAF wild type.

b. Patients must have received only 1 prior line of therapy with single-agent anti-PD-1 or anti-PD-L1 therapy, which must be their most recent anti-cancer treatment. Patients must not have received anti-CTLA-4 alone or in combination with anti-PD-1 or anti-PD-L1. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

c. Patients are not eligible who received adjuvant or first-line therapy for advanced/metastatic disease consisting of molecular target therapies including, but not limited, to BRAF, MEK, or C-KIT targeted therapies (single agent or in any combination), or intralesional therapy.

d. Patients are not eligible who received doublet immuno-oncology therapy, including checkpoint inhibitors combined with either systemic or intralesional therapy. Patients are not eligible who received cytotoxic chemotherapy such as dacarbazine, paclitaxel or others.

e. Patients must have confirmed radiographic or biopsy-proven disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 therapy.

f. Patients must consent to providing pre-study scans (if available) to confirm radiographic progression.

Cohort 1d – Melanoma (1L, following prior adjuvant therapy)

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

b. Patient must have received prior adjuvant therapy for melanoma; adjuvant therapy may consist of any immuno-oncology regimens (single-agent or combination therapy) or molecularly targeted therapy (such as tyrosine kinase inhibitors). The disease-free interval from last dose of adjuvant therapy to a diagnosis of advanced or metastatic melanoma must be less than 180 days.

Cohort 1e − Melanoma

a. Patients who were enrolled under an earlier version of the protocol who are no longer eligible for Cohorts 1a through 1d.

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.

Cohort 2b − RCC (2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory)

a. Patients must have received only 1 prior line of therapy with an anti-PD-1 or anti-PD-L1 containing regimen, which must be their most recent anti-cancer treatment. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

b. Patients must have confirmed radiographic disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 containing regimen. Patients must consent to providing pre-study scans (if available) to confirm radiographic progression.

Cohort 2c – Renal Cell Carcinoma

a. Patients who were enrolled under an earlier version of the protocol who are no longer eligible for Cohorts 2a or 2b.

17. Non-Small Cell Lung Cancer (NSCLC)

a. Histologically confirmed or cytologically confirmed diagnosis of stage IV NSCLC (unless otherwise noted)

b. Patients with nonsquamous NSCLC must lack both epidermal growth factor receptor (EGFR)-sensitizing mutation/deletion and anaplastic lymphoma kinase (ALK) translocation by local testing (assessment of ROS1 mutation status is not required, unless otherwise noted). For ALK or EGFR testing, an FDA-approved test or validated assay should be used as applicable for selection of patients. For patients with squamous NSCLC, testing for EGFR, ALK, or ROS1 is not required.

Cohorts 3a.1, 3a.2, 3a.3, and 3a.4 − NSCLC (1L)

a. Patients must have known PD-L1 status as per validated immunohistochemistry testing. Up to 20 efficacy-evaluable patients will be enrolled in each subgroup of PD-L1 negative (PD-L1 < 1%; Cohort 3a.1), PD-L1 highly positive (PD-L1 ≥ 50%; Cohort 3a.3), or PD-L1 low/intermediate (PD-L1 ≥ 1% - < 50%; Cohort 3a.2). For patients who do not have known PD-L1 status, testing must be done using an FDA-approved PD-L1 test. An abbreviated consent may be presented to the patient prior to the Screening period to permit early assessment of the PD-L1 status of the tissue sample. Patients enrolled in Cohort 3a who do not have a PD-L1 status assessed by central testing will be assigned to Cohort 3a.4.

b. Patients must not have received prior anti-cancer therapy for advanced or metastatic NSCLC; patients must not have received prior immuno-oncology in any setting (including neoadjuvant, adjuvant, locally advanced or metastatic disease).

Cohort 3b − NSCLC (2L, I-O therapy naive) following platinum-based therapy

a. Patients must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease. Patients are not eligible who refused prior platinum-based therapy.

b. Patients who received platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.

c. Patients must not have received any prior immuno-oncology in any setting 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.

Cohort 3c − NSCLC (2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory)

a. Patients must have received only 1 prior line of therapy with anti-PD-1 or anti-PD-L1 therapy. Patients are eligible if they received sequential therapy (e.g., cytotoxic chemotherapy followed by anti PD-1 or anti PD-L1 therapy, or vice versa). Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

b. Patients must not have received anti-CTLA-4 alone or in combination with anti-PD-1 or anti-PD-L1, unless the anti-CTLA-4 therapy stopped > 1 year prior to Cycle 1 Day 1.

c. Prior to the anti-PD-1 or anti-PD-L1 therapy regimen, patients must have received zero or 1 prior line of cytotoxic chemotherapy for metastatic disease.

d. Patients must have confirmed radiographic disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 containing regimen. Patients must consent to providing pre-study scans (if available) to confirm radiographic progression.

e. Patients may not have primary immuno-oncology refractory disease (radiographic or clinical progression within 120 days of initiation of immuno-oncology therapy).

Cohorts 3d.1 and 3d.2 − NSCLC (1L nonsquamous) (in combination with platinum/pemetrexed and maintenance pemetrexed [Cohort 3d.1] or without maintenance pemetrexed [Cohort 3d.2])

a. Patients must have nonsquamous NSCLC. The patient will be excluded if the histology is considered predominantly squamous cell NSCLC. Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the patient is ineligible.

b. Patients must not have received prior anti-cancer therapy for advanced or metastatic NSCLC; patients who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the development of metastatic disease. Patients must not have received prior immuno-oncology therapy in any setting (including neoadjuvant, adjuvant, locally advanced or metastatic disease).

c. Patients must be candidates for platinum/pemetrexed chemotherapy and willing to take folic acid and vitamin B_{12} supplementation.

d. Patients must not have received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of study medication.

Cohort 3e − NSCLC (1L squamous) (in combination with platinum/taxane)

a. Patients must have squamous NSCLC.

b. Patients must not have received prior anti-cancer therapy for advanced or metastatic NSCLC; patients who received adjuvant or neoadjuvant chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy are eligible. Patients must not have received prior immuno-oncology therapy in any setting (including neoadjuvant, adjuvant, locally advanced or metastatic disease).

c. Patients must be candidates for platinum/taxane chemotherapy.

d. Patients must not have received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of study medication.

e. Known hypersensitivity to the selected cytotoxic chemotherapy study drugs.

Cohort 3f − NSCLC (3L+, ALK-translocation/ROS1 rearrangement positive)

a. Patients must have ALK-translocation positive or ROS1 rearrangement NSCLC by local pathology report (assessment of ROS1 mutation status is not required). For ALK testing, an FDA-approved test or validated assay must be used.

b. Patients must have received at least two prior anti-cancer therapies for advanced or metastatic NSCLC (these may have included chemotherapy and must have included at least one ALK-directed and/or ROS-1-directed therapy), be ineligible to receive these therapies due to toxicity, or no longer be considered a candidate for additional tyrosine kinase inhibitor therapy; patients must not have received prior immuno-oncology therapy in any setting (including neoadjuvant, adjuvant, locally advanced or metastatic disease).

c. Patients may not have received more than one prior cytotoxic-based regimen (e.g., carboplatin with paclitaxel).

Cohort 3g − NSCLC (3L+, EGFR mutation/deletion)

a. Patients must have EGFR mutation or relevant deletion NSCLC by local pathology report. For EGFR testing, an FDA-approved test or validated assay should be used.

b. Patients must have received at least two prior anti-cancer therapies for advanced or metastatic NSCLC (these may have included chemotherapy and must have included at least one EGFR-directed small molecule therapy), be ineligible to receive these therapies due to toxicity, or no longer be considered a candidate for additional tyrosine kinase inhibitor therapy; patients must not have received prior I-O therapy in any setting (including neoadjuvant, adjuvant, locally advanced or metastatic disease).

c. Patients may not have received more than one prior cytotoxic-based regimen (e.g., carboplatin with paclitaxel).

Cohort 3h − NSCLC (2L, anti PD 1 or anti PD L1 relapse/refractory)

a. Patients must have received only 1 prior line of therapy with anti-PD-1 or anti-PD-L1 therapy in combination with doublet platinum-containing cytotoxic chemotherapy, which must be their most recent anti-cancer treatment. Patients are not eligible if they received sequential therapy (e.g., cytotoxic chemotherapy doublet therapy followed by anti PD-1 or anti PD-L1 therapy or vice versa). Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

b. Patients must not have received more than 1 prior line of cytotoxic chemotherapy for metastatic disease.

c. Patients must have confirmed radiographic disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 containing regimen. Patients must consent to providing pre study scans (if available) to confirm radiographic progression.

d. Patients may not have primary immuno-oncology refractory disease (radiographic or clinical progression within 120 days of initiation of immuno-oncology therapy).

Cohort 3i – NSCLC

a. Patients who were enrolled under an earlier version of the protocol who are no longer eligible for Cohorts 3a.1 to 3h.

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.

Cohort 4b – Urothelial Carcinoma (2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory)

a. Patients must have progressed on only one prior line of therapy that contains platinum-based chemotherapy in the metastatic setting or post platinum-based chemotherapy in an adjuvant setting with progression < 6 months.

b. Patients must have received only one prior line of therapy with single-agent anti-PD-1 or anti-PD-L1 therapy, which must be their most recent anti-cancer treatment. Patients must not have received anti-CTLA-4 alone or in combination with anti-PD-1 or anti-PD-L1. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

c. Patients must have confirmed radiographic disease progression at least 4 weeks after initial disease progression, or unequivocal radiographic progression as per the Investigator based on a single imaging assessment; this assessment must be within 90 days from last dose of anti-PD-1 or anti-PD-L1 therapy. Patients must consent to providing pre-study scans (if available) to confirm radiographic progression.

d. Patients may not have primary immuno-oncology refractory disease (radiographic or clinical progression within 120 days of initiation of immuno-oncology therapy).

Cohort 4c − Urothelial

a. Patients who were enrolled under an earlier version of the protocol who are no longer eligible for Cohorts 4a or 4b.

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

a. Patients must have diagnosis of advanced triple-negative breast cancer (TNBC) ("advanced" is defined either locally advanced breast cancer not amenable to curative surgery or radiotherapy or distant metastases).

- Less than 1% of tumor cell nuclei test positive for estrogen and progesterone receptors determined by using standard IHC
- Human epidermal growth factor receptor 2 (HER2) negative as determined by local pathologist, using IHC or in situ hybridization
- Patients must have had triple negative phenotype of breast cancer in all available biopsies that have been examined during the course of the disease.

b. Patients must have received 0 or 1 prior line of therapy with systemic cytotoxic chemotherapy for advanced TNBC or patient refuses standard of care. Substitution within a class of anti-cancer therapy (e.g., nab-paclitaxel for paclitaxel; carboplatin for cisplatin) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received 1 prior line of therapy.

c. Patients are excluded whose disease-free interval (for patients with prior neoadjuvant or adjuvant chemotherapy: the interval between the last dose of neoadjuvant or adjuvant chemotherapy to the diagnosis of advanced breast cancer; for patients originally diagnosed with Stage I/II/III breast cancer who did not receive prior neoadjuvant or adjuvant chemotherapy: the interval between date of original diagnosis of breast cancer and date of diagnosis of advanced breast cancer) is less than 6 months and no clinically significant tumor-related symptoms in the judgment of the investigator. Patients with a diagnosis of de novo Stage IV breast are eligible.

d. Patients are excluded if the screening LDH > 2 × ULN (based on the central laboratory).

e. Must not have received any prior 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-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.

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

a. Patients must be candidates for NKTR-214 in combination with nivolumab.

Cohort 5b − Triple-Negative Breast Cancer (1-2L, I-O therapy naive) in combination with nab-paclitaxel

a. Patients must be candidates for single-agent nab-paclitaxel; patients may not have received paclitaxel or docetaxel for metastatic carcinoma and may not have relapsed with metastatic disease within 1 year of adjuvant paclitaxel or docetaxel treatment.

b. Patients may not have received prior nab-paclitaxel in any setting.

Cohort 5c − Triple-Negative Breast Cancer (1-2L, I-O therapy naive) in combination with eribulin

a. Patients must be a candidate for single-agent eribulin; patients may not have relapsed with metastatic disease within 1 year of adjuvant taxane-based treatment.

b. Patients may not have received prior eribulin in any setting.

Cohort 5d – TNBC

a. Patients who were enrolled under an earlier version of the protocol who are no longer eligible for Cohorts 5a to 5c.

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

a. Patients must have diagnosis of advanced hormone-receptor positive breast carcinoma ("advanced" is defined either locally advanced breast cancer not amenable to curative surgery or radiotherapy or metastatic disease).

- ≥ 1% of tumor cell nuclei test positive for estrogen or progesterone receptors determined by using standard IHC
- HER2 negative as determined by local pathologist, using IHC or in situ hybridization
- For patients whose primary tumor was HER2-positive or hormone-receptor positive, eligibility will be based on the first biopsy for advanced disease.

b. Patients must have either archival or fresh tumor biopsy that demonstrates ≥ 1% positive PD-L1 staining by the central pathology laboratory. An abbreviated consent may be presented to the patient prior to the Screening period to permit early assessment of the PD-L1 status of the tissue sample.

c. Patients must have received prior aromatase inhibitor and fulvestrant therapy for advanced breast cancer. (Progression after prior adjuvant therapy with an aromatase inhibitor within 12 months will count as a line of therapy). Hormonal therapy may have been administered as single-agent or in combination with CDK4-6 inhibitors (such as palbociclib and others), mTOR inhibitors (everolimus and others), PI3K inhibitors (buparlisib and others), or other agents used in combination with hormonal agents (AKT inhibitors, WNT inhibitors, or others).

d. Must not have received any prior 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-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.

Cohort 6a − Hormone-Receptor Positive, HER2-Negative Breast Cancer (I-O therapy naive following hormonal therapy)

a. Patients must not have received prior cytotoxic chemotherapy (such as tubulin-targeting agents (paclitaxel, docetaxel, nab-paclitaxel, eribulin, vinca alkaloids, epothilones, and others), anti-metabolites (5-fluorouracil, capecitabine, gemcitabine, and others), platinum agents (carboplatin, cisplatin, and others), alkylating agents (cyclophosphamide and others), topoisomerase 1 or 2 inhibitors (irinotecan, doxorubicin, epirubicin, etoposide, and others) or VEGF-targeted monoclonal antibodies (bevacizumab and others). Prior systemic therapy must be reviewed by the Medical Monitor prior to registration for the trial.

Cohort 6b − Hormone-Receptor Positive, HER2-Negative Breast Cancer (I-O therapy naive following hormonal and cytotoxic therapy)

a. Patients must have received at least one and up to 2 prior lines of cytotoxic chemotherapy (such as tubulin-targeting agents (paclitaxel, docetaxel, nab-paclitaxel, eribulin, vinca alkaloids, epothilones, and others), anti-metabolites (5-fluorouracil, capecitabine, gemcitabine, and others), platinum agents (carboplatin, cisplatin, and others), alkylating agents (cyclophosphamide and others), topoisomerase 1 or 2 inhibitors (irinotecan, doxorubicin, epirubicin, etoposide, and others). Substitution within a class of anti-cancer therapy (e.g., carboplatin for cisplatin) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received a prior line of therapy. Prior systemic therapy must be reviewed by the Medical Monitor prior to registration for the trial.

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

a. Patients must have diagnosis of advanced gastric adenocarcinoma or gastroesophageal carcinoma (GC) (“advanced” is defined either locally recurrent surgically unresectable advanced cancer or metastatic disease).

b. Patients must have either archival or fresh tumor biopsy that demonstrates PD-L1 staining (Combined Positive Score ≥ 1 as determined by an FDA-approved test or validated assay). An abbreviated consent may be presented to the patient prior to the Screening period to permit early assessment of the PD-L1 status of the tissue sample.

c. Patients must have received no more than two prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy, and (if appropriate) HER2-targeted systemic therapy for gastric cancer. These drugs may have been administered in the neoadjuvant, adjuvant, locally advanced or metastatic setting. Patients may have progressed or been intolerant to these therapies. (“Systemic therapy” includes all agents, including cytotoxic, molecularly targeted or other). Substitution within a class of anti-cancer therapy (e.g., capecitabine for fluorouracil

[5-FU]; carboplatin for cisplatin) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received a prior line of therapy.

d. Must not have received any prior 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-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.

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

a. Patients must have diagnosis of advanced colorectal carcinoma (CRC) ("advanced" is defined either locally advanced unresectable cancer or metastatic disease).

b. Patients must have either archival or fresh tumor biopsy that demonstrates microsatellite instability (MSI) high or mismatch repair deficient (dMMR) disease. An abbreviated consent may be presented to the patient prior to the Screening period to permit early assessment of the CD8+ TIL status of the tissue sample.

c. Patients who had disease progression during, after, or were intolerant to, prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy (patients must have received either fluoropyrimidine and oxaliplatin-containing chemotherapy OR fluoropyrimidine and irinotecan-containing chemotherapy for colorectal carcinoma cancer ("FOLFOX" [fluorouracil, leucovorin, and oxaliplatin] or "FOLFIRI" [5-fluorouracil, leucovorin, and irinotecan]); and (if appropriate) EGFR-targeted and/or VEGF-targeted systemic therapy. These drugs may have been administered in the neoadjuvant, adjuvant, locally advanced or metastatic setting. ("Systemic therapy" includes all agents, including cytotoxic, molecularly targeted or other). Substitution within a class of anti-cancer therapy (e.g., capecitabine for 5-FU) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received a prior line of therapy.

d. Must not have received any prior 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-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.

Cohort 8b – Colorectal Carcinoma (3-4L, I-O therapy naive); MSI-non-high

a. Patients must have diagnosis of advanced colorectal carcinoma (CRC) ("advanced" is defined either locally advanced unresectable cancer or metastatic disease).

b. Patients must have either archival or fresh tumor biopsy that demonstrates MSI not high (MSI-stable or MSI-low) or mismatch repair proficient (pMMR) disease. In addition, tumor tissue must demonstrate CD8+ tumor infiltrating lymphocytes (≥ 10% by IHC) by central laboratory. An abbreviated consent may be presented to the patient prior to the Screening period to permit early assessment of the CD8+ TIL status of the tissue sample.

c. Patients must have received at least two but no more than 3 prior lines of therapy including fluoropyrimidine-, oxaliplatin and irinotecan-containing chemotherapy colorectal cancer; and (if appropriate) EGFR-targeted and/or VEGF-targeted systemic therapy. These drugs may have been administered in the neoadjuvant, adjuvant, locally advanced or metastatic setting. ("Systemic therapy" includes all agents, including cytotoxic, molecularly targeted or other). Substitution within a class of anti-cancer therapy (e.g., capecitabine for 5-FU) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received a prior line of therapy.

d. Must not have received any prior 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-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.

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

a. Patients must have diagnosis of limited-stage or extensive-stage SCLC.

b. Patients must have received no more than 1 prior line of platinum-based therapy. Substitution within a class of anti-cancer therapy (e.g., carboplatin for cisplatin) is permitted; otherwise patients who discontinued therapy for reasons other than progressive disease are still considered to have received a prior line of therapy.

c. Must not have received any prior 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-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.

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

Under Amendment 7, the study is closed to patient screening and enrollment.

For Disease-Specific Tumor Types

24. **Cohorts 10a.1 and 10a.3 − Renal Cell Carcinoma (1L), as follows:**

- Cohort 10a.1: concurrent dosing schedule 1 (this cohort was closed to enrollment under Amendment 6.0)
- Cohort 10a.3: concurrent dosing schedule 3

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.

c. Patients must not have received prior anti-cancer therapy for advanced or metastatic RCC.

d. 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.

25. **Cohort 11a.1 − Non-Small Cell Lung Cancer (1L)**

a. Histologically confirmed or cytologically confirmed diagnosis of stage IV NSCLC

b. Patients with nonsquamous NSCLC must lack both epidermal growth factor receptor (EGFR)-sensitizing mutation/deletion and anaplastic lymphoma kinase (ALK) translocation by local testing (assessment of ROS1 mutation status is not required). For ALK or EGFR testing, an FDA-approved test or validated assay should be used as applicable for selection of patients. For patients with squamous NSCLC, testing for EGFR and ALK is not required.

c. Patients must not have received prior anti-cancer therapy for advanced or metastatic NSCLC.

d. Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.

26. **Cohorts 12a.2 and 12a.3 − Melanoma (1L), as follows:**

- Cohort 12a.2: concurrent dosing schedule 2
- Cohort 12a.3: concurrent dosing schedule 3

a. Histologically confirmed stage III (unresectable) or stage IV melanoma, as per American Joint Committee on Cancer (AJCC) staging system.

b. Patients must consent to BRAF testing or have documented BRAF status as per regionally acceptable V600 mutational status testing.

c. Uveal melanoma will be excluded.

d. Have not received prior anti-cancer therapy for advanced or metastatic melanoma.

e. 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.

f. Prior to disease metastasis, patients must not have received neoadjuvant or adjuvant tyrosine kinase (BRAF, MEK, mTOR), bevacizumab or intralesional therapy.

27. **Cohort 13a.2 – Urothelial Carcinoma (1L)**

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.

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.

4.2 Exclusion Criteria

Under Amendment 7, the study is closed to patient screening and enrollment.

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).

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 7).

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.

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. If the patient's weight has changed more than 10% from the Cycle 1 Day 1 weight, the dose of NKTR-214 must be recalculated and subsequent weight measurements should be compared with this new baseline weight to determine if further NKTR-214 dose recalculations are necessary.

When administered on the same day, NKTR-214 will be administered first before nivolumab, ipilimumab, or other anti-cancer therapy. NKTR-214 will be administered IV over 30 (± 5) minutes at a starting dose of 0.006 mg/kg every 3 weeks (± 3 days). Patients should be carefully monitored for infusion reactions during NKTR-214 administration. If an acute infusion reaction is noted, patients should be managed according to Section 5.15.

Nivolumab administration should start at least 30 minutes from the end of NKTR-214 administration. It is highly recommended that ipilimumab administration should start within 30 minutes after completion of nivolumab administration.

The ipilimumab infusion is set at 30 minutes for both the 1 mg/kg and 3 mg/kg doses. 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 (± 5) minutes at either a 360 mg flat dose q3w (Parts 2, 3, and 4); 1 mg/kg q3w × 4 doses or 3 mg/kg q3w × 4 doses (Parts 3 and 4)
- Parts 3 and 4: Ipilimumab (anti-CTLA-4) administered IV over 30 (± 5) minutes at 1 mg/kg q6w, 1 mg/kg q3w × 4 doses or 3 mg/kg q3w × 4 doses (Parts 3 and 4)
- Part 2: Cohort 3d.1 (NSCLC): NKTR-214 followed by nivolumab (q3w) followed by investigator's choice of cisplatin 75 mg/m^2 administered IV or carboplatin AUC 5 with pemetrexed 500 mg/m^2 q3w by IV administration for 4 cycles followed by maintenance NKTR-214, nivolumab, and pemetrexed
- Part 2: Cohort 3d.2 (NSCLC): NKTR-214 followed by nivolumab (q3w) followed by investigator's choice of cisplatin 75 mg/m^2 administered IV or carboplatin AUC 5 with pemetrexed 500 mg/m^2 q3w by IV administration for 4 cycles followed by maintenance NKTR-214 and nivolumab (see Section 5.13.12 for treatment discontinuation criteria of maintenance NKTR-214 and nivolumab).
- Part 2: Cohort 3e (NSCLC): NKTR-214 followed by nivolumab (q3w) followed by either Cremophor-based paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle or nab-paclitaxel 100 mg/m^2 by IV infusion on Days 1, 8, and 15 of each 21-day cycle for 4 cycles with either carboplatin AUC 6 administered IV on cycle Day 1 q3w for 4 cycles or cisplatin 75 mg/m^2 q3w for 4 cycles followed by maintenance NKTR-214 and nivolumab (see Section 5.13.12 for treatment discontinuation criteria of maintenance NKTR-214 and nivolumab).
- Part 2: Cohort 5b (TNBC): NKTR-214 followed by nivolumab (q3w) followed by nab-paclitaxel 260 mg/m^2 q3w by IV administration
- Part 2: Cohort 5c (TNBC): NKTR-214 followed by nivolumab (q3w) followed by eribulin mesylate 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2) by IV administration on Days 1 and 8 q3w; dose modification based on liver function tests should be made as outlined in the Package Insert or Summary of Product Characteristics.

5.3.2 Part 1: Dose Escalation

Dose escalation is described in Table 5 and will be carried out as listed in Table 6.

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
- 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 5: 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 6: 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 7). Any DLT past the DLT window is a delayed DLT.

Table 7: 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 6). 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.

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 8 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 8 has been assessed in 38 patients.

Table 8: 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.

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, 21 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).

5.3.3.1 Update of Safety and Efficacy Data for Protocol Amendment 6 (dated 18 June 2018)

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 24 patients who received the RP2D in the dose escalation phase, including 7 with metastatic melanoma, 14 with renal cell carcinoma (RCC), and 3 with NSCLC (Table 9). Of these 24 response-evaluable patients, 15 patients (62.5%) had partial or complete responses and 5 (20.8%) had stable disease.

Table 9: 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 936 patients will be enrolled (Table 10). 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.

Part 2 is closed to patient screening and enrollment under Amendment 7.0.

Table 10: Part 2 Treatment Cohorts (All Patients Receive NKTR-214 plus Nivolumab[a])

Part 2 Cohorts: All Patients Receive NKTR-214 plus Nivolumab[a]		
Indication	Cohort	Description
Melanoma	1a[b]	1L
	1b[b]	2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory
	1c[c]	2L, BRAF wild type anti-PD-1 or anti-PD-L1 relapse/refractory
	1d[c]	1L, following prior adjuvant therapy
	1e	Patients enrolled under an earlier protocol version who are no longer eligible for Cohorts 1a to 1d
RCC	2a[b]	1L
	2b[c]	2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory
	2c	Patients enrolled under an earlier protocol version who are no longer eligible for Cohorts 2a or 2b
NSCLC	3a.1[f]	1L, PD-L1< 1%
	3a.2[f]	1L, PD-L1 ≥ 1% - < 50%
	3a.3[f]	1L, PD-L1 ≥ 50%
	3a.4[f]	1L, PD-L1 status unknown
	3b[d]	2L, I-O therapy naïve following platinum-based therapy
	3c[c]	2L-3L, anti-PD-1 or anti-PD-L1 relapse/refractory
	3d.1[f]	1L, nonsquamous in combination with platinum/pemetrexed (+ maintenance pemetrexed)
	3d.2[f]	1L, nonsquamous in combination with platinum/pemetrexed (no maintenance pemetrexed)
	3e[f]	1L squamous in combination with platinum/taxane
	3f[e]	3L+, ALK-translocation/ROS1 rearrangement positive
	3g[e]	3L+, EGFR mutation/deletion
	3h[f]	2L, following platinum-based doublet cytotoxic chemotherapy combined with anti-PD-1
	3i	Patients enrolled under an earlier protocol version who are no longer eligible for Cohorts 3a.1 to 3h
Urothelial	4a[d]	1L, cisplatin ineligible
	4a[d,g]	1L, refused standard of care
	4b[c]	2-3L, anti-PD-1 or anti-PD-L1 relapse/refractory
	4c	Patients enrolled under an earlier protocol version who are no longer eligible for Cohorts 4a and 4b
TNBC	5a[b]	1-2L, I-O therapy naive
	5b[c]	1-2L, I-O therapy naive in combination with nab-paclitaxel
	5c[c]	1-2L, I-O therapy naive in combination with eribulin
	5d	Patients enrolled under an earlier protocol version who are no longer eligible for Cohorts 5a to 5c

Table 10: Part 2 Treatment Cohorts (All Patients Receive NKTR-214 plus Nivolumab[a]) (Cont'd)

Part 2 Cohorts: All Patients Receive NKTR-214 plus Nivolumab[a]		
Indication	Cohort	Description
HR+ HER2- BC	6a[c]	I-O therapy naive following hormonal therapy
	6b[c]	I-O therapy naive following hormonal and cytotoxic therapy
Gastric	7[d]	2-3L, I-O therapy naive
CRC	8a[c]	2-3L, I-O therapy naive; MSI-high
	8b[c]	3-4L, I-O therapy naive; MSI-non-high
SCLC	9[e]	2L, I-O therapy naive

Abbreviations: CRC = colorectal carcinoma; 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 closed under Amendment 5.1.
c. Cohorts closed with an administrative letter dated 29 March 2019.
d. Cohorts closed under Amendment 6.
e. Cohorts never opened for screening.
f. Cohorts closed with an administrative letter dated 22 January 2020.
g. 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 (see Section 9.3). 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)

Patients receive NKTR-214 followed by nivolumab (q3w) followed by investigator's choice of cisplatin 75 mg/m^2 administered IV or carboplatin AUC 5 with pemetrexed 500 mg/m^2 q3w by IV administration for 4 cycles. Following the fourth cycle, Cohort 3d.1 will continue to receive NKTR-214, nivolumab, and pemetrexed at a dose of 500 mg/m^2 q3w as maintenance therapy and Cohort 3d.2 will receive NKTR-214 and nivolumab maintenance, but not pemetrexed. Patients receive premedication with folic acid, vitamin B_{12}, and glucocorticoids administered according to local guidelines for pemetrexed use. Unless otherwise stipulated at the medical center, the following supportive care should be used:

- Dexamethasone should be administered at a dose of 4 mg by mouth twice daily the day before, the day of, and the day after pemetrexed administration.
- At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed; and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Patients must receive one intramuscular injection of vitamin B_{12} (1000 μg) during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as pemetrexed.

5.3.4.1.2 Cohort 3e: NSCLC (1L squamous)

Patients in this cohort will be treated for a total of 4 cycles of NKTR-214 followed by nivolumab (q3w) followed by either Cremophor-based paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle or nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, and 15 of each 21-day cycle with investigator's choice of either carboplatin AUC 6 IV on cycle Day 1 q3w for 4 cycles or cisplatin 75 mg/m^2 q3w for 4 cycles. Following the fourth cycle, Cohort 3e will continue to receive NKTR-214 and nivolumab maintenance. Standard supportive care for infusion-related reactions may be administered.

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

Patients receive NKTR-214 followed by nivolumab (q3w) followed by nab-paclitaxel 260 mg/m^2 by IV administration q3w. Standard supportive care for infusion-related reactions may be administered.

5.3.4.1.4 Cohort 5c: TNBC in Combination with Eribulin

Patients receive NKTR-214 followed by nivolumab (q3w) followed by eribulin mesylate 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2) by IV administration on Days 1 and 8 q3w. Dose modification for patients with baseline liver function test abnormalities should follow the Package Insert or Summary of Product Characteristics. Standard supportive care for infusion-related reactions may be administered.

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

The safety and tolerability of NKTR-214 in combination with nivolumab and ipilimumab will be evaluated in approximately 36 1L patients with metastatic or advanced RCC, NSCLC, melanoma, or urothelial carcinoma.

Dose schedules and scenarios for triplet therapy are summarized in Table 11. The dose-limiting toxicity (DLT) evaluation period for the triplet therapy (NKTR-214/nivolumab/ipilimumab) will begin with the first dose of ipilimumab and the evaluation period will be a minimum of 3 weeks (21 days).

Cohort A (concurrent dosing) is the first schedule to be evaluated with administration of all 3 study drugs on the same day (NKTR-214/nivolumab/ipilimumab) (Table 11). The Cohort A maintenance dose will be administered continuously after the last dose of ipilimumab for dosing schedules 2 and 3 following the 4 doses of nivolumab and ipilimumab. The first patient in each of the 3 dosing schedules listed in Table 12 will be enrolled and assessed for 7 days prior to the enrollment of patients 2 to 6 in each dosing schedule. Based on emerging safety and biomarker data from Cohort A, Cohort B may be explored for the following scenarios:

- For each of the 3 dosing schedules, unless the safety profile of the triplet combination is deemed unacceptable by the sponsor and investigators.
- If available biomarker data from the patients in Cohort A indicate sub-optimal T cell activation with concurrent dosing.

For either Cohort A or B, the dose levels of NKTR-214 for a given dosing schedule may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested. The DLT evaluation period for the NKTR-214/nivolumab/ipilimumab triplet therapy will begin with the first dose of ipilimumab and the evaluation period will be a minimum of 3 weeks (21 days). DLT evaluation will be based on the study dose schedule as detailed in Section 5.11.

Part 3 is closed to patient screening and enrollment under Amendment 7.

Table 11: Example of Concurrent and Staggered Schedule Scenarios for Triplet (Dosing Schedule 1)

Cohort	C1D1	C2D1	C3D1	C4D1	C5D1[a]
A (concurrent)	NKTR-214 nivolumab ipilimumab	NKTR-214 nivolumab	NKTR-214 nivolumab ipilimumab	NKTR-214 nivolumab	NKTR-214 nivolumab ipilimumab[b]
B (staggered)	NKTR-214 nivolumab	NKTR-214 nivolumab	NKTR-214 nivolumab ipilimumab	NKTR-214 nivolumab	NKTR-214 nivolumab ipilimumab[b]

Abbreviations: C1D1 = Cycle 1 Day 1; C2D1 = Cycle 2 Day 1; C3D1 = Cycle 3 Day 1, etc.

a. Only the first 5 cycles are shown

b. Ipilimumab will be continuously dosed q6w (as shown in Table 11) or q3w only for 4 doses based on assigned dosing schedule.

Table 12: Part 3, Cohort A: Concurrent Dosing Schedules

Dosing Schedules	Indication	N[a]	NKTR-214 q3w	Nivolumab q3w	Ipilimumab q3w or q6w	Maintenance Dose[b] q3w
1	RCC[c]	12	0.006 mg/kg	360 mg flat dose	1 mg/kg q6w	n/a
	NSCLC[d]					
2	Urothelial[d]	12	0.006 mg/kg	1 mg/kg × 4 doses	3 mg/kg q3w × 4 doses	NKTR-214 0.006 mg/kg + nivolumab 360 mg
	Melanoma[d]					
3	RCC[d]	12	0.006 mg/kg	3 mg/kg × 4 doses	1 mg/kg q3w × 4 doses	
	Melanoma[d]					

a. Enrollment will be up to 12 patients.

b. NKTR-214 at 0.006 mg/kg and nivolumab at 360 mg will be dosed continuously q3w after the last dose of ipilimumab for dosing schedules 2 and 3 following the 4 doses of nivolumab and ipilimumab.

c. This cohort is a historical cohort for both concurrent and staggered dosing and was closed to patient enrollment under Amendment 6.

d. Cohorts closed with an administrative letter dated 22 January 2020.

The Safety Review Committee will jointly decide the following:

- Dose and schedule for the next cohort
- RP2D
- Dose levels of NKTR-214, for a given dosing schedule, may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested.
- Decision for a recommended phase 2 dose schedule will be determined by both safety and pharmacological parameters.
- Decision to evaluate the triplet in additional patients at lower doses and/or different dose schedules within the anticipated 36 patients to better assess the benefit/risk profile

The Sponsor may choose to concurrently enroll patients at lower dose levels and/or different dose schedules to assess the benefit/risk profile within the anticipated 36 patients. In Part 3, the RP2Ds will be established for each of the 3 dosing schedules (it may be necessary for a separate RP2D be established for patients with melanoma and urothelial cancers, if the tolerability is different between these 2 groups). When an RP2D is established in Part 3, enrollment for that dosing schedule will begin in Part 4. The sponsor will decide which dosing schedules will be opened in Part 4.

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

Enrollment into the dose expansion cohorts will commence once the RP2D for the triplet has been established in Part 3 for each respective tumor type. The maximum of patients in each cohort is listed in Table 25 (based on a Historical and Target ORR); the total will include any patients from each of the 6 cohorts in Part 3, thus approximately 106 additional patients may be enrolled into Part 4 (Table 13). Patients will be enrolled simultaneously to each indication; for patients with melanoma, enrollment will occur simultaneously with dose schedule assigned alternately based on date of screening until one of the respective dosing schedule's enrollment is fulfilled.

Part 4 is closed to patient screening and enrollment under Amendment 7.0.

Table 13: Part 4 Indications and Dosing Schedules

Indication	Cohort	Concurrent Dosing Schedule[a]
RCC	10a.1[b]	1
	10a.3[d]	3
NSCLC	11a.1[d]	1
Melanoma	12a.2[d]	2
	12a.3[c]	3
Urothelial	13a.2[d]	2

a. If staggered dosing is to be tested, matching cohorts will be named as follows: the letter 'a' will be substituted with 'b' (e.g., for the urothelial indication, concurrent dosing Cohort 13a.2 will be named staggered dosing Cohort 13b.2).

b. This cohort is a historical cohort for both concurrent and staggered dosing and was closed to patient enrollment under Amendment 6.

c. This cohort was closed with an administrative letter on 29 March 2019.

d. Cohorts closed with an administrative letter dated 22 January 2020.

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).

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 7.16 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.

Adequate hydration mitigates the development of hypotension associated with NKTR-214 administration. Hydration and renal function must be assessed within 24 hours, or as soon as locally feasible, prior to each study drug administration (see Appendix 1B for the list of analytes that require collection and evaluation prior to study drug administration). For patients who must delay study treatment due to creatinine increase, see additional information regarding criteria to delay (Sections 5.13.1 to 5.13.3), resume (Section 5.13.11), or permanently discontinue study treatment (Section 5.13.12). Underlying reasons for decreased oral intake (e.g., nausea) should be addressed and treatment (e.g., IV hydration) should be provided. The Investigator may modify these recommendations based on the needs of the individual patient. Patients will also be provided a handout with hydration guidance.

Patients should be administered 1 liter of IV fluids on the day of each dosing of NKTR-214. For the next 3 days (Days 2–4) after NKTR-214 administration, instruct patients to drink at least 2 liters per day of self-administered oral hydration. Advise patients to restrain from activity that may contribute to dehydration (including, but not limited to, strenuous activity, long hot showers, and saunas) for Days 1 to 4 of every cycle of NKTR-214 treatment. Per clinical judgment, IV fluids may be administered in any cycle. The Investigator may decide to forego administering IV fluids to a patient or adjust the recommendation for self-administered oral hydration to a particular patient if this is deemed in the best interest of the patient (e.g., evidence of fluid overload). Advise participants with orthostatic symptoms to call their treating oncologist and consider increasing oral hydration.

Patients with pre-existing adrenal impairment requiring corticosteroid supplementation may be at increased risk for hypotensive episodes during treatment with NKTR-214 (Section 5.13.4).

Between Days 3 and 5, inclusive, following administration of the first two doses of NKTR-214 in Cycles 1 and 2, site personnel must contact the patient (by telephone or clinic visit) to remind the patient of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion (Section 1.2). In subsequent NKTR-214 administrations in Cycle 3 and beyond, the oral hydration follow-up should be conducted as clinically indicated for patients receiving the NKTR-214/nivolumab doublet (with or without other anti-cancer therapies) in Part 2; the oral hydration follow-up is mandatory for patients receiving the NKTR-214/nivolumab/ipilimumab triplet in Parts 3 or 4 following study drug administration in any cycle.

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
- 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, including following radiotherapy or surgery on a target lesion, 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 or radiotherapy/surgery on a target lesion 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.

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 the last study therapy used in the study is permanently discontinued or before a new antineoplastic regimen starts, whichever occurs earlier.

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).

5.4.1 Patients in Cohort 3d or Cohort 3e

Patients enrolled in Cohorts 3d or 3e who discontinue NKTR-214 and/or nivolumab may remain on study and continue to receive the other protocol-defined anticancer therapies.

5.5 Long-Term Follow-up

Long-term follow-up should continue until withdrawal of consent, death, lost to follow-up, or study termination by the Sponsor. At the long-term follow-up visits, data will be collected regarding toxicity, as well as information related to start of new anticancer therapy and survival. See also Section 7.5 and Section 7.8. Timing for long-term follow-up will be as follows:

- Long-term follow-up visits should occur every 30 (+ 10) days for 3 visits after the last dose of any of the study treatment medications (whichever is the last to be administered), then every 90 (± 10) days, or as needed for data deliverables for survival status, which may be captured by telephone contact. However, if the date of decision to discontinue all study drugs is greater than 40 days from the last dose of any study treatment medication, long-term follow-up visits should begin from the date of EOT decision. In addition, a safety follow-up visit should take place 100 days after the last administration of nivolumab/ipilimumab; this visit may be combined with the 90-day visit with the window of ± 10 days. Per clinical judgment, the patient may come in earlier. The long-term follow-up visit and EOT visit may occur on the same date. When these two visits occur on the same date, all the requirements of the EOT visit and the long-term follow-up visits should be fulfilled.

- All patients will be contacted for survival and information about initiation of new anticancer therapy every 3 months. Survival follow up should continue until patient withdrawal of consent for survival follow up, death, loss to follow-up, or study termination by the Sponsor.

- 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.

- A sample for immunogenicity testing for NKTR-214 will be collected at the first 30-day follow up visit.

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. .

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, a scan is recommended no sooner than 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. [redacted]

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 (nivolumab only): 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, it is advised that additional PK blood samples are 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.), EOT, and the first 30-day follow-up visit.
>
> For all other Parts of the study except Part 1, immunogenicity samples will be collected according to the Appendix 2 Schedule of Assessments.

Immunogenicity samples for nivolumab/ipilimumab will be drawn as follows:

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.

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.

Serum samples for immunogenicity assessments 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)

Refer to the Laboratory Manual for specific instructions on sample processing, storage, and shipping.

[redacted]

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 optional tumor biopsy may be collected during Days 15-21 (Week 3) 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.

Pretreatment and on-treatment biopsies should be taken from the same lesion, if feasible. Biopsies should only 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.

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 7. 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 resolve 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.

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 7. 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 administration can continue in the absence of NKTR-214-related toxicity that would warrant a dose delay and once the criteria to resume are met (Section 5.13.11). If the Investigator cannot determine which study drug is causing the toxicity, then all study drugs should be delayed.

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, except for fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or total bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
    - Grade ≥ 3 AST, ALT, total bilirubin will require dose discontinuation.

- Patient has acute infection (e.g., fever, upper or lower respiratory tract infection) requiring systemic antibiotic therapy. Patient may resume study treatment once free of signs or symptoms for 72 hours after completion of antibiotic therapy (See Section 5.13.11).

- Any AE, laboratory abnormality, or inter-current illness that, in the judgment of the Investigator, warrants delaying the dose of study medication.

Patients who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met. Dose delays of up to 6 weeks are permitted.

5.13.2 Ipilimumab Dose Delay Criteria

Dose reductions for ipilimumab are not permitted in this study. Dose delays are permitted for ipilimumab. Per recommendation of the Investigator and approval of the Sponsor's Medical Monitor, ipilimumab may be delayed based on observed drug-related toxicities. If ipilimumab is delayed, NKTR-214 or nivolumab administration can continue in the absence of NKTR-214- or nivolumab-related toxicity that would warrant a dose delay and once the criteria to resume are met (Section 5.13.11). If the Investigator cannot determine which study drug is causing the toxicity, then all study drugs should be delayed.

Ipilimumab must be delayed for the following reasons.

- 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.

5.13.3 NKTR-214 Dose Delay and Reduction Criteria

Dose delays and reductions are permitted for NKTR-214. Per recommendation of the Investigator, NKTR-214 may be delayed or reduced (to 0.003 mg/kg) based on observed drug-related toxicities. Medical Monitor consultation is required for dose reduction. If the NKTR-214 dose is reduced to 0.003 mg/kg, the dose should remain at this level throughout the remainder of the study. 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 and once the criteria to resume are met (Section 5.13.11).

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

- For persistent Grade 2 drug-related toxicity, at the discretion of the Investigator, with the exception of:
  - Grade ≥ 2 creatinine increase:
    - For patients who must delay study treatment due to Grade ≥ 2 creatinine increase due to a non-inflammatory cause, delay retreatment with study drug for approximately 3 to 5 days. After the dosing delay, the patient may resume study drug when serum creatinine has returned to Grade ≤ 1, as assessed within 24 hours prior to redosing. For further guidance, refer to the Renal AE Management Algorithm in current Nivolumab Investigator's Brochure.

- Patient has acute infection (e.g., fever, upper or lower respiratory tract infection) requiring systemic antibiotic therapy. Patient may resume study treatment once free of signs or symptoms for 72 hours after completion of antibiotic therapy (See Section 5.13.11)
- Grade ≥ 3 toxicity at least possibly related to NKTR-214: NKTR-214 dosing must be delayed until resolution to Grade 1 or baseline (unless otherwise requiring permanent discontinuation, per Section 5.13.12), with the following exceptions:
  - Grade ≥ 3 lymphopenia
  - Grade ≥ 3 asymptomatic amylase or lipase elevation

NKTR-214 dosing may resume at the same dose or at a lower dose 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 (see Section 5.13.12 for permanent discontinuation criteria).

5.13.4 Monitoring and Management of Adrenal Insufficiency and Hypophysitis

Adrenal insufficiency and hypophysitis have been observed in patients receiving nivolumab and ipilimumab. Consider prompt evaluation when patients have signs or symptoms of hypophysitis or adrenal insufficiency which includes levels of early-morning ACTH, cortisol, thyroid-stimulating hormone (TSH), and free thyroxine (T4). Co-management with an endocrinologist is recommended for patients with pre-existing adrenal insufficiency.

5.13.5 Monitoring and Management of NKTR-214-induced Eosinophilia

Frequent and significant eosinophilia has been observed in patients receiving NKTR-214, primarily starting at Cycle 2 or later, consistent with the known effect of IL-2 therapy. Clinical data analysis demonstrated that frequency of selected AEs (primarily Grade 1 or 2 in severity) such as rash, pruritus, edema, nausea, vomiting, diarrhea, and dizziness increased with level of eosinophilia. Isolated cases of hypereosinophilic syndrome and other eosinophilic disorders have been reported.

Absolute eosinophil count (AEC) should be closely monitored per protocol. If a study patient is suspected to have eosinophilic disorder (symptoms may involve skin, lungs, digestive tract, heart, blood, and nervous systems) with AEC at or above 5000/μL (5×10^9/L) level, NKTR-214 treatment may need to be withheld, and the patient should be treated as clinically indicated.

5.13.6 Monitoring and Management of Elevated Hepatic Transaminases

Elevated hepatic transaminases are an overlapping toxicity that can occur for both NKTR-214 and nivolumab. The elevations in hepatic transaminases associated with NKTR-214 typically occur at the time of peak active cytokine concentration in the blood (Days 2-4), and are often accompanied by other cytokine-related toxicities such as flu-like symptoms, rash or pruritus. The transient elevations in hepatic transaminases are usually mild or moderate in severity, not associated with increased total bilirubin, resolve spontaneously without treatment, and predominantly occur in Cycle 1 and Cycle 2. Grade 3 abnormalities with these characteristics have been observed in PIVOT-02 study during Cycle 1, and patients were able to continue study treatment uninterrupted with close laboratory monitoring.

Hepatic events, including elevated liver function tests, have also been observed for nivolumab. Most cases were of low or moderate severity. Higher grade abnormalities are concerning for immune mediated hepatitis, and typically occur with a later onset (median time to onset of 3.3 months) (nivolumab package insert). Immune-mediated hepatitis generally results in a quick rise in liver function tests, and responds to corticosteroids or immune-modulating agents. **For transaminase elevations occurring in Cycle 2 onwards potentially involving an immune-mediated mechanism, follow the immune-mediated hepatic adverse event management guidelines in the current nivolumab Investigator's Brochure or package insert for appropriate management.**

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

Dose delays and reductions are required for hematological and non-hematological toxicity. Recommended dose modifications for key chemotherapy toxicities are outlined in Table 14, Table 15, and Table 16. These serve as a guide and do not replace investigator judgment and applicable local label recommendations.

Table 14: Dose Levels for Platinum and Pemetrexed

Drug	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	75 mg/m^2	56 mg/m^2	38 mg/m^2	Discontinue
Carboplatin	AUC 5, maximum dose 750 mg	AUC 3.75, maximum dose 562.5 mg	AUC 2.5, maximum dose 375 mg	Discontinue
Pemetrexed	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue

Table 15: Recommended Dose Modifications for Hematologic Toxicity for Platinum and Pemetrexed

		Pemetrexed	Platinum
Platelets	**ANC**	**DOSE LEVEL**	
$\geq 50 \times 10^3/\mu L$ AND	$\geq 0.5 \times 10^3/\mu L$	Dose Level 0	Dose Level 0
$\geq 50 \times 10^3/\mu L$ AND	$< 0.5 \times 10^3/\mu L$	Dose Level -1	Dose Level -1
$< 50 \times 10^3/\mu L$ without bleeding AND	ANY	Dose Level -1	Dose Level -1
$< 50 \times 10^3/\mu L$ with $\geq$ Grade 2 bleeding AND	ANY	Dose Level -2	Dose Level -2
ANY AND	< 1.0 + fever $\geq$ 38.5°C (101°F)	Dose Level -1	Dose Level -1

Table 16: Recommended Dose Modifications for Non-Hematologic Toxicity for Platinum and Pemetrexed

Event	CTC Grade	Pemetrexed	Cisplatin	Carboplatin
		DOSE LEVEL		
Nausea or vomiting	3 or 4	Dose Level 0	Dose Level 0	Dose Level 0
Diarrhea	3 or 4	Dose Level -1	Dose Level -1	Dose Level 0
Mucositis	3 or 4	Dose Level -2	Dose Level 0	Dose Level 0
Neurotoxicity	2	Dose Level 0	Dose Level -2	Dose Level 0
Neurotoxicity	3 or 4	Discontinue	Discontinue	Dose Level -1
Transaminase Elevation	3	Dose Level -1	Dose Level -1	Dose Level -1
Transaminase Elevation	4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	3 or 4	Dose Level -1	Dose Level -1	Dose Level -1

Abbreviations: CTC = common terminology criteria

Creatinine clearance (CrCl) will be based on the original weight-based Cockcroft and Gault formula. CrCl must be ≥ 45 mL/min prior to the administration of chemotherapy. Pemetrexed and/or cisplatin may be delayed for up to 42 days to allow the patient time to recover from the toxicity. If a patient′s CrCl value has not returned to ≥ 45 mL/min within 42 days after the previous dose, cisplatin and/or pemetrexed must be discontinued.

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

Dose delays and reductions are required for hematological and non-hematological toxicity. Recommended dose modifications for key chemotherapy toxicities are outlined in Table 17, Table 18, and Table 19. These serve as a guide and do not replace investigator judgment and applicable local label recommendations.

Table 17: Dose Levels Platinum and Taxane

Drug	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	75 mg/m^2	56 mg/m^2	38 mg/m^2	Discontinue
Carboplatin	AUC 6	AUC 4.5 or 5	AUC 3 or 4	Discontinue
Nab-Paclitaxel	100 mg/m^2	75 mg/m^2	50 mg/m^2	Discontinue
Paclitaxel	200 mg/m^2	175 mg/m^2	150 mg/m^2	Discontinue

Table 18: Recommended Dose Modifications for Hematologic Toxicity Platinum and Taxane

Platelets	ANC	Nab-Paclitaxel	Platinum
		DOSE LEVEL	
≥ 50 × 10^3/μL AND	≥ 0.5 × 10^3/μL	Dose Level 0	Dose Level 0
≥ 50 × 10^3/μL AND	< 0.5 × 10^3/μL	Dose Level -1	Dose Level -1
ANY AND	Delay of initiation of next cycle by > 7 days due to < 1.5 × 10^3/μL	Dose Level -1	No change
< 50 × 10^3/μL without bleeding AND	ANY	Dose Level -1	Dose Level -1
< 50 × 10^3/μL with ≥ Grade 2 bleeding AND	ANY	Dose Level -2	Dose Level -2
ANY AND	< 1.0 + fever ≥ 38.5°C (101°F)	Dose Level -1 Dose Level -2 (2nd episode) Discontinue (3rd episode)	Dose Level -1

Table 19: Recommended Dose Modifications for Non-Hematologic Toxicity Platinum and Taxane

Event	CTC Grade	Nab-Paclitaxel or Paclitaxel	Cisplatin	Carboplatin
		DOSE LEVEL		
Nausea or vomiting	3 or 4	Dose Level 0	Dose Level 0	Dose Level 0
Diarrhea	3 or 4	Dose Level -1	Dose Level -1	Dose Level 0
Neurotoxicity	2	Dose Level -1	Dose Level -2	Dose Level 0
Neurotoxicity	3 or 4	Dose Level -1 or -2 Dose Level -2 (2nd episode)	Discontinue	Dose Level -1 or -2 Dose Level -2 (2nd episode)
Transaminase Elevation	3	Dose Level -1	Dose Level -1	Dose Level -1
Transaminase Elevation	4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	3 or 4	Dose Level -1	Dose Level -1	Dose Level -1

CrCl will be based on the original weight-based Cockcroft and Gault formula. CrCl must be ≥ 45 mL/min prior to the administration of cisplatin. Nab-paclitaxel, paclitaxel, and/or platinum may be delayed for up to 42 days to allow the patient time to recover from the toxicity. If a

patient′s CrCl value has not returned to ≥ 45 mL/min within 42 days after the previous dose, cisplatin must be discontinued.

5.13.9 Nab-Paclitaxel Dose Delay and Reduction Criteria

Dose delays and reductions are for hematological and non-hematological toxicity. For these, please refer to country specific approved product label for dose modifications (Abraxane package insert).

5.13.10 Eribulin Dose Delay and Reduction Criteria

Dose delays and reductions are required for hematological and non-hematological toxicity.

The administration of eribulin should be delayed on Day 1 or Day 8 for any of the following:

- Absolute neutrophil count (ANC) < $1 \times 10^3/\mu L$
- Platelets < $75 \times 10^3/\mu L$
- Grade 3 or 4 non-hematological toxicities

These recommendations in Table 20 serve as a guide and do not replace investigator judgment and applicable local label recommendations.

Table 20: Dose Recommendations for Eribulin

Adverse Reaction After Previous Administration	Recommended Dose
Hematological:	1.1 mg/m^2 (eribulin mesylate) 0.97 mg/m^2 (eribulin)
ANC < 0.5 × 10^3/μL lasting more than 7 days	
ANC < 1 × 10^3/μL neutropenia complicated by fever or infection	
Platelets < 25 × 10^3/μL l thrombocytopenia	
Platelets < 50 × 10^3/μL thrombocytopenia complicated by hemorrhage or requiring blood or platelet transfusion	
Non-hematological:	
Any Grade 3 or 4 in the previous cycle OR omission or delay of Day 8 dose in previous cycle for toxicity	
Reoccurrence of any hematological or non-hematological adverse reactions as specified above:	
Despite reduction to 1.1 mg/m^2 (eribulin mesylate); 0.97 mg/m^2 (eribulin)	0.7 mg/m^2 (eribulin mesylate) 0.62 mg/m^2 (eribulin)
Despite reduction to 0.7 mg/m^2 (eribulin mesylate); 0.62 mg/m^2 (eribulin)	Consider discontinuation

5.13.11 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 5.13.12. 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 who delayed dosing for acute infection requiring systemic antibiotic therapy must be free of signs or symptoms of infection for 72 hours after completion of antibiotic therapy prior to resuming study treatment.
- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients who have not experienced a Grade 3 drug-related skin AE may resume study treatment in the presence of Grade 2 skin toxicity.
- 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 5.13.12) should have treatment permanently discontinued.
- 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. Grade ≥ 3 adrenal insufficiency or Grade ≥ 4 hypophysitis require discontinuation regardless of control with hormone replacement (see Section 5.13.12 for permanent treatment discontinuation criteria). Hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should not require discontinuation.
- 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.
- For patients who must delay study treatment due to Grade ≥ 2 creatinine increase due to a non-inflammatory cause (see Sections 5.13.1, 5.13.2, and 5.13.3), delay retreatment with study drug for approximately 3 to 5 days. After the dosing delay, the patient may resume study drug when serum creatinine has returned to Grade ≤ 1, as assessed within 24 hours, or as soon as locally feasible, prior to redosing with study drug, except where permanent discontinuation of study drug is required (see Section 5.13.12).
- Dose delay of NKTR-214 that results in treatment delay of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 5.13.12. 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 5.13.12), 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.

For patients in Parts 3 and 4 (NKTR-214 plus nivolumab plus ipilimumab), treatment with NKTR-214 plus nivolumab may continue if patients experience toxicities or are unable to tolerate ipilimumab.

5.13.12 Permanent Treatment Discontinuation Criteria

Patients meeting any of the following criteria will be required to permanently discontinue all assigned study drug(s). However, per the investigator's assessment, treatment with NKTR-214 or with nivolumab alone may continue if the toxicities listed below are considered not related to the respective drug, or are considered related to ipilimumab and/or other anti-cancer study drugs only once the criteria to resume are met (Section 5.13.11). For CVA events and suspected TIA

events, follow the criteria described below (additional details are provided in the CVA management algorithm in Appendix 3).

- 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).
- Grade 3 or 4 infusion reaction of any duration that occurs during the:
  - NKTR-214 infusion or prior to the nivolumab infusion requires discontinuation of NKTR-214.
  - Nivolumab infusion or later requires discontinuation of both NKTR-214 and nivolumab.
- 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, endocrinopathies, and laboratory abnormalities:
  - Grade 3 drug-related uveitis, pneumonitis, myocarditis, bronchospasm, diarrhea, colitis, neurologic toxicity, or hypersensitivity reaction **of any duration** requires discontinuation.
  - Grade 3 drug-related endocrinopathies (excluding adrenal insufficiency) adequately controlled with only physiologic hormone replacement do not require discontinuation.
    - Note: For Grade ≥ 3 adrenal insufficiency, treatment needs to be discontinued regardless of control with hormone replacement (hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should 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 (except adrenal insufficiency or hypophysitis) such as, 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 per investigator discretion.
    - Note: For Grade ≥ 3 adrenal insufficiency or Grade ≥ 4 hypophysitis, treatment needs to be discontinued regardless of control with hormone replacement (hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should not require discontinuation).
- 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.

- Any new CVA event confirmed by imaging (diffusion-weighted imaging [DWI] MRI is preferred, unless contraindicated), regardless of neurological symptoms (see Appendix 3):
  - For patients in Parts 3 or 4 receiving triplet immunotherapy: discontinue study treatment.
  - For patients in Part 2 receiving doublet immunotherapy: study treatment may be continued only after careful risk-benefit assessment by the Investigator.

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 AEs related to the following organs/systems (including, but may not be limited to):

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Myocarditis

  and

- Neurological

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

Infusion reactions have been 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. Infusion

reactions should be graded as outlined below (consistent with CTCAE v4.03 grading of infusion-related reactions; please also refer to 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, ipilimumab, or NKTR-214 will be permanently discontinued (see Section 5.13.12). 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. Additionally, document medications or other therapeutic measures administered for SAEs occurring within 100 days of last dose of nivolumab or ipilimumab (see Section 7.7).

5.17 Permitted Concomitant Medications/Treatment

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 and may require co-management with an endocrinologist (see Section 5.13.4). 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. Short-term use of systemic corticosteroids or immunosuppressive medication is permitted if administered for AE treatment.

Prophylaxis for flu-like symptoms with either acetaminophen or ibuprofen is permitted on study per the Investigator's discretion (as appropriate, additional treatment measures may be provided based on local treatment standards and guidelines, see Section 5.15). 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 (as appropriate, additional treatment measures may be provided based on local treatment standards and guidelines, see Section 5.15). 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 only on non-target lesions and only after discussion with the Medical Monitor. On-study radiotherapy to target lesions is not permitted.

If a patient receives radiotherapy or surgery on a target lesion, the patient may be allowed to continue in the study (if written request is received from the study investigator) and may remain on study treatment for as long as there is clinical benefit as assessed by the investigator and in consultation with the medical monitor.

5.18 Prohibited and/or Restricted Concomitant Medications

5.18.1 Prohibited 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 or equivalent.
- Any antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, investigational agent, or radiation therapy [except as described in Section 5.17]) is prohibited during the study.

- Any live / attenuated vaccines *(*e.g., varicella zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR], or Flumist® Quadrivalent*)* are not allowed during study treatment and until 100 days after the last dose of study drug. Vaccination with inactivated viruses is permitted consistent with the institutional guidelines. Allow appropriate time interval between the most recent study treatment administration and the next date of study treatment. If the patient experiences side effects post flu vaccine or other inactivated vaccine, please manage study treatment administration per protocol guideline.

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.

5.18.2 Blood Pressure Medications

Consideration should be given to withholding 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 withholding antihypertensive medications, withhold no less than 12 hours and no more than 48 hours prior to each dose of NKTR-214.

Patients who are on medications with antihypertensive effects for the treatment of coronary artery disease (e.g., beta-blockers, calcium channel blockers, nitrates, etc.) should be able to withhold these drugs.

Antihypertensive medications may be reinitiated in between doses of NKTR-214 at any time as clinically indicated (i.e., based on blood pressure monitoring results).

For patients receiving beta-blockers, consider a step-wise tapering of doses before initiation of NKTR-214 to avoid reflex tachycardia. If Grade ≥ 2 hypertension is observed in any cycle, patients should be monitored more frequently (at least weekly) until a new stable antihypertensive regimen is identified. Patients may be monitored more frequently at the discretion of the investigator as clinically warranted.

5.18.3 Effect of NKTR-214 on the PK of Concomitant Medications

NKTR-214 may have the potential to affect the PK of co-administered drugs based on its intended pharmacology as a modulator of immune function. NKTR-214 causes increases in circulating cytokines typical of those associated with an acute inflammatory response to infection or tissue injury. The increases in inflammatory cytokines induced by NKTR-214 are generally moderate, persist for about one week after NKTR-214 dosing, and return to baseline levels prior to the next dose. Several of these cytokines (IFN-γ, IL-6, IL-10, etc.) have the potential to decrease the activity of multiple enzymes and drug transporters, and the suppressive effects can be additive (Haas, 2005; Zidek, 2009). Similar to changes that occur during a typical

inflammatory response, NKTR-214 may lead to down regulation of drug metabolizing enzymes, such as CYP enzymes, hepatic flavin monooxygenases, UDP-glucuronosyltransferases, sulfotransferases, and glutathione S-transferases. Consequently, treatment with NKTR-214 may lead to temporary decrease in clearance of drugs that are substrates of these Phase I and Phase II drug metabolizing enzymes, or drug transporters. Clinicians should carefully monitor patients who receive drugs with narrow therapeutic indices or drugs that are sensitive substrates of drug metabolizing enzymes or drug transporters for occurrence of adverse effects, and adjust the dose if needed.

5.19 Adverse Events

All AEs, either reported by the patient or observed by study staff, will be reported from the time of first study drug(s) administration until 100 days after the last dose of all study drug(s). 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). For SAEs, additional reporting requirements also apply (see Section 7.7).

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.

6.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

6.1 NKTR-214 Drug Description and Formulation

[redacted]

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

[redacted]

[redacted]

6.4 NKTR-214 Drug Storage

[redacted]

6.5 NKTR-214 Drug Shipment

[redacted]

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. Commercially available nivolumab and/or ipilimumab may be obtained with reimbursement. For other anti-cancer study drugs, commercially available supplies should be locally procured. Please refer to the Pharmacy Manual for details.

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 Site Drug Accountability Log, a copy of which must be given to Nektar Therapeutics at the end of the study.

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

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 from the time of first study drug(s) administration until 100 days after the last dose of all study drug(s). For SAEs, additional reporting requirements also apply (see Section 7.7).

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.

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:

- 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 will be reported from the time of first study drug(s) administration until 100 days after the last dose of all study drug(s). For patients initiating a new antineoplastic regimen, the decision date of study drug discontinuation and the EOT visit date must be prior to the start date of the new antineoplastic regimen.

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 as described above. 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.

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 relationship to study drugs, that occur during the protocol-specified reporting period, must be reported with the exception of deaths attributed to disease progression (refer to Section 7.9). 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, regardless of causality attribution, will be reported to Nektar Therapeutics Drug Safety within **24 hours** of when the site becomes aware of the event. The duration of the reporting period is described in Section 7.5, AE Reporting and Follow-up.

For SAEs that occur within 100 days of last dose of nivolumab or ipilimumab, medications and other therapeutic measures used to treat the SAE will be recorded on the eCRF.

In addition, all SAEs that occur beyond 100 days after the last dose of all study drug(s) that are assessed by the Investigator as 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 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 on the SAE Report Form.

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.

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 and Death due to Disease Progression – Not Reportable as an AE/SAE

It is anticipated that during this study a proportion of patients will experience disease progression prior to study discontinuation. Progressive disease (PD) in some patients may result in hospitalization or death. Such events leading to hospitalization or death of a study patient are typically considered "serious," requiring submission of an SAE report. However, because PD is an endpoint for this study, reporting the term "disease progression" as either an AE or SAE is not necessary.

However, if there are separate identifiable clinical manifestations of the PD, (e.g., pleural effusion or weight loss), the primary manifestations may be reported as non-fatal AEs or SAEs. For all SAEs associated with fatal PD, the following criteria will apply:

- *Seriousness Criteria = Cannot equal Death*
- *Severity = Cannot equal Grade 5*
- *Outcome = Ongoing at time of Death*

7.10 Immune-mediated Adverse Events

Nektar will evaluate imAEs associated with either NKTR-214, nivolumab, and/or ipilimumab. Investigators should use clinical judgment when 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.

See Section 5.14 for additional information on management algorithms for immune mediated AEs.

7.11 Adverse Events of Special Interest

Cerebrovascular accident (CVA, any grade) is considered an "adverse event of special interest" (AESI) and should be assessed for seriousness using the standard seriousness definition. However, all CVAs are required to follow the timeline for SAE reporting (within 24 hours as described in Section 7.7) from the sites to Nektar Drug Safety: pharmacovigilance@nektar.com. CVA Management Guidelines are provided in Appendix 3.

7.12 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 7.7 for reporting details).

A potential DILI is defined as:

- Treatment-emergent ALT or AST > 3 times ULN,

AND

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

AND

- 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.

7.13 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 up to 5 months for female patients or 7 months for female partners of male patients after the last dose of the study drug(s) via the Pregnancy 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. In order for the Sponsor or designee to collect any pregnancy surveillance information, the pregnant patient or partner must sign an informed consent form for disclosure information. Information on this pregnancy will be collected on the Pregnancy Form. Female patient(s) or female partner(s) of male 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.

If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed at the discretion of the investigator (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended) following approvals of the patient/IRB/IEC, as applicable.

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

7.15 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, Cycle 1 Day 2 (C1D2), C1D3, C1D8, 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.

7.16 Vital Signs

Vital sign measurements will be recorded according to the Schedule of Assessments (Appendix 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.

7.17 Electrocardiograms

Prior to each NKTR-214 PK sampling time in Cycle 1 of treatment, 5 minutes of ECG data will be recorded (for details 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.

7.18 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 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.

7.19 Pregnancy Tests

Serum or urine 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, or for female patients who reach 1 year of postmenopausal status after study entry (or reach 5 month post-surgical sterilization after entering the study).

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 7.13.

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.

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. CT/PET is acceptable providing the CT component is of diagnostic quality (with slice thickness ≤ 10 mm). 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 < 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 21 provides the definitions of the criteria used to determine objective tumor response for target lesions.

Table 21: 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 22 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 22: 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).

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 23: 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

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.

9.1.1 Efficacy

All efficacy endpoints except OS and PFS will be analyzed using the response evaluable population and the ITT population. OS and PFS will be reported for the ITT population. 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.

During Part 3, cohorts of at least 6 patients will be enrolled to each of the 3 dosing schedules in Cohort A (concurrent dosing). Additional patients will be added to each dose schedule based on the scheme and rules outlined in Section 5.3.5 or Sponsor determination of the need for additional data to further evaluate the benefit/risk profile. If a DLT is observed in 2 or more patients of 6 in Cohort A, patients may enroll into Cohort B (staggered dosing), where ipilimumab will be staggered to be administered at a later cycle (e.g., Cycle 3 Day 1). It is estimated that approximately 36 patients will be enrolled into the Part 3 dose escalation phase.

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 24 and Table 25). 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 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.

Table 24: True (Target) and Historic Objective Response Rate for Each Indication in Part 2

Cohort[a]	Indication	Objective Response Rate (%)		Sample Size[b]			Futility		Efficacy		Reference for Historical ORR Assumption
		Historical	Target	N1	N2	Total	S1	S2	T1	T2	
1a	MEL 1L	40	65	13	15	28	≤ 5	≤ 14	≥ 10	≥ 15	Robert, 2015
1b	MEL 2-3L, I-O relapse/ refractory	10	30	15	11	26	≤ 1	≤ 5	≥ 4	≥ 6	Unmet medical need
1c	MEL 2L BRAF wild type I-O relapse/ refractory	10	30	15	11	26	≤ 1	≤ 5	≥ 4	≥ 6	Unmet medical need
1d	MEL 1L following prior adjuvant therapy	10	30	16	12	28	≤ 1	≤ 5	≥ 4	≥ 6	Nomura, 2017; Weber, 2013
2a	RCC 1L	25	50	11	15	26	≤ 2	≤ 9	≥ 6	≥ 10	Topalian, 2012
2b	RCC 2-3L, I-O relapse/ refractory	5	25	15	11	26	≤ 0	≤ 3	≥ 3	≥ 4	Unmet medical need
3a	NSCLC regardless of PD-L1 expression	23	45	16	18	34	≤3	≤11	≥7	≥12	Garon 2015; Gettinger 2016; Carbone, 2017
3a.1	NSCLC 1L PD-L1 < 1%	8	30	12	8	20	≤ 0	≤ 3	≥ 3	≥ 4	Garon, 2015; Carbone, 2017
3a.2	NSCLC 1L PD-L1 ≥ 1%-< 50%	14	40	8	10	18	≤ 0	≤ 4	≥ 4	≥ 5	
3a.3	NSCLC 1L PD-L1 ≥ 50%	25	55	11	9	20	≤ 3	≤ 7	≥ 6	≥ 8	
3b	NSCLC 2L, I-O therapy naive following platinum-based therapy	20	40	20	16	36	≤ 4	≤ 10	≥ 8	≥ 11	Brahmer, 2015
3c	NSCLC 2L, I-O relapse/refractory	5	20	12	25	37	≤0	≤3	≥3	≥4	Unmet medical need
3d.1	NSCLC, 1L nonsquamous (+ maintenance pemetrexed)	45	66	20	19	39	≤ 9	≤ 21	≥ 14	≥ 22	Gandhi, 2018
3d.2	NSCLC, 1L nonsquamous (no maintenance pemetrexed)	45	66	20	19	39	≤ 9	≤ 21	≥ 14	≥ 22	Gandhi, 2018
3e	NSCLC 1L squamous in combination with platinum/taxane	20	40	20	16	36	≤ 4	≤ 10	≥ 8	≥ 11	Rizvi, 2016

Table 24: True (Target) and Historic Objective Response Rate for Each Indication in Part 2 (Contd)

Cohort[a]	Indication	Objective Response Rate (%)		Sample Size[b]			Futility		Efficacy		Reference for Historical ORR Assumption
		Historical	Target	N1	N2	Total	S1	S2	T1	T2	
3f	3L+ NSCLC ALK-translocation/ ROS1 rearrangement positive	5	20	12	25	37	≤0	≤3	≥3	≥4	Unmet medical need
3g	3L+ NSCLC, EGFR mutation/deletion	5	20	12	25	37	≤0	≤3	≥3	≥4	Unmet medical need
4a	Urothelial 1L Cis-ineligible	16	45	10	8	18	≤1	≤5	≥4	≥6	Balar, 2017
	Urothelial 1L (refused standard of care)	16	45	10	8	18	≤1	≤5	≥4	≥6	
4b	Urothelial 2-3L, I-O relapse/ refractory	5	25	13	7	20	0	≤2	≥3	≥3	Patel, 2018
5a	TNBC 1-2L, I-O therapy naïve	10	26	21	17	38	≤ 1	≤ 6	≥ 5	≥ 7	Schmid, 2017
5b	TNBC 1-2L, I-O therapy naive + nab-paclitaxel	24	45	20	18	38	≤ 5	≤ 12	≥ 9	≥ 13	Forero-Torres, 2015; Gradishar, 2005
5c	TNBC 1-2L, I-O therapy naive + eribulin	20	40	20	16	36	≤ 4	≤ 10	≥ 8	≥ 11	Kaufman, 2015; McIntyre, 2014
6a	HR+ breast cancer, I-O therapy naive following hormonal therapy	25 (cytotoxic chemo-therapy)	45	18	21	39	≤ 5	≤ 14	≥ 9	≥ 15	Harris, 2006; Twelves, 2014
		5% (for single agent CPI)	20	12	25	37	0	≤ 3	≤ 3	≥ 4	Rugo 2016; Dirix 2018
6b	HR+ breast cancer, I-O therapy naive following hormonal and cytotoxic therapy	20 (cytotoxic chemo-therapy)	40	20	16	36	≤ 4	≤ 10	≥ 8	≥ 11	Harris, 2006; Twelves, 2014
		5% (for single agent CPI)	20	12	25	37	0	≤ 3	≤ 3	≥ 4	Rugo 2016; Dirix [redacted]

Table 24: True (Target) and Historic Objective Response Rate for Each Indication in Part 2 (Contd)

Cohort[a]	Indication	Objective Response Rate (%)		Sample Size[b]			Futility		Efficacy		Reference for Historical ORR Assumption
		Historical	Target	N1	N2	Total	S1	S2	T1	T2	
7	Gastric carcinoma 2-3L, I-O therapy naïve	13	30	22	15	37	≤ 2	≤ 7	≥ 7	≥ 8	Kang, 2017
8a	CRC 2-3L, MSI-high, I-O therapy naïve	30	50	26	13	39	≤ 7	≤ 15	≥ 13	≥ 16	Overman, 2017
8b	CRC 3-4L, MSI-non-high, I-O therapy naïve	5	20	12	25	37	≤ 0	≤ 3	≥ 3	≥ 4	Le, 2015 (mismatch repair proficient)

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

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

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

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

Two interim analyses will be conducted in Cohort 3h to gate the trial progression based on the ITT Population (see Section 9.5). The first interim evaluation will be conducted when 20 evaluable patients have been followed for 4 months or terminated from the study. If 3 or more responses are observed, the trial may continue to the next stage. The second interim analysis will be performed when 40 evaluable patients have been followed for 4 months or terminated from the study. If there are 6 or more responders, the trial may continue to enroll approximately 100 patients. Enrollment will continue without pause during the conduct of the interim analyses.

Approximately 936 patients will be enrolled into Part 2. Additional patients may be added to selected expansion cohorts to further evaluate the benefit/risk profile or the Sponsor may choose not to open or complete all expansion cohorts.

Approximately 36 patients will be enrolled into Part 3.

Approximately 106 additional patients will be enrolled into Part 4.

Table 25: True (Target) and Historic Objective Response Rate for Each Indication in Parts 3 and 4

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

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

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

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

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 during the Dose Escalation phase of the trial 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

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

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.

Any interim efficacy analysis based on the ITT population will exclude ongoing patients who do not have any post-baseline efficacy assessment due to insufficient follow-up.

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/schedule (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.

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 using the response evaluable population. Except as stated otherwise in the SAP, the ORR based on the Investigator's assessment will be the primary efficacy endpoint and will be summarized using the response evaluable population. ORR will also be summarized for the ITT population based on an independent radiology review. Any interim efficacy analysis based on the ITT population will exclude ongoing patients who do not have any post-baseline efficacy assessment due to insufficient follow-up. 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 target-lesion tumor-directed radiotherapy and target-lesion tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent antineoplastic therapy as described. 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, will be summarized similarly to ORR using the response evaluable population and the ITT population.

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 is first. For patients who 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, or had surgery or radiotherapy to the target lesion prior to disease progression per RECIST 1.1, patients will be censored on the date of last evaluable tumor assessment prior to receiving new treatment. 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. Additional censoring rules will be discussed in the SAP.

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

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.

[redacted]

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 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.

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.

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

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.

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.

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.

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.

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.

15.0 REFERENCES

1. Abraxane [package insert]. Summit, NJ: Celgene Corporation; 2015.

2. Abraxane Summary Basis of Approval https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21660_ABRAXANE_medr.PDF

3. Algazi A, Tsai KK, Takamura KT, et al. Intratumoral electroporation of plasmid IL-12 can prime response to anti-PD1/PD-L1 blockade in patients with Stage III/IV-M1a melanoma. Abstract CT134. Presented at the 2016 annual Meeting of the American Association for Cancer Research, 16-20 April 2016, New Orleans, LA.

4. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017;389:67-76.

5. Boyman O, Sprent J. The role of interleukin-2 during homeostasis and activation of the immune system. Nat Rev Immunol. 2012;12:180-190.

6. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373:123-35.

7. Brayer J, Fishman M. Regression of metastatic clear cell kidney cancer with interleukin-2 treatment following nivolumab (anti-PD-1) treatment. J Immunother. 2014;37:187-191.

8. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med. 2017;376:2415-26.

9. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomized study. Lancet. 2011;377:914-23.

10. Daud AI, Loo K, Pauli ML, et al. Tumor immune profiling predicts response to anti-PD-1 therapy in human melanoma. J Clin Invest. 2016a;126:3447-3452.

11. Daud AI, Wolchok JD, Robert C, et al. Programmed death-ligand 1 expression and response to the anti-programmed death 1 antibody pembrolizumab in melanoma. J Clin Oncol. 2016b;34:4102-4109.

12. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. Breast Cancer Res Treat. 2018;167(3):671-86.

13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247.

14. Fleming TR. One-sample multiple testing procedure for phase II clinical trials. Biometrics. 1982;38:143-51.

15. Forero-Torres A, Varley KE, Abramson VG, et al. Translational Breast Cancer Research Consortium (TBCRC). TBCRC 019: A Phase II Trial of Nanoparticle Albumin-Bound Paclitaxel with or without the Anti-Death Receptor 5 Monoclonal Antibody Tigatuzumab in Patients with Triple-Negative Breast Cancer. Clin Cancer Res. 2015 Jun 15;21(12):2722-9.

16. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018; doi: 10.1056/NEJMoa1801005. [Epub ahead of print].

17. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372:2018-28.

18. Gassenmaier M, Lipp HP, Scheu A, et al. Safety of shortened infusion times for combined ipilimumab and nivolumab. Cancer Immunol Immunother. 2018;67:135-140.

19. Gettinger S, Rizvi NA, Chow LQ, Borghaei H, Brahmer J, Ready N, Gerber DE, Shepherd FA, Antonia S, Goldman JW, Juergens RA. Nivolumab monotherapy for first-line treatment of advanced non–small-cell lung cancer. Journal of Clinical Oncology. 2016 Sep 1;34(25):2980.

20. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005;23:7794-803.

21. Haas CE, Nelsen JL. Drug-cytokine interactions. In Piscitelli SC, Rodvold KA, eds. Drug Interactions in Infectious Diseases. Human Press Inc, Totowa NJ, USA. 2005 pp 431-61.

22. Harris LN, Broadwater G, Lin NU, et al. Molecular subtypes of breast cancer in relation to paclitaxel response and outcomes in women with metastatic disease: results from CALGB 9342. Breast Cancer Research. 2006;8(6):R66.

23. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387:1540-50.

24. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390:2461-71.

25. Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015;33:594-601.

26. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch repair deficiency. N Engl J Med. 2015;372:2509-20.

27. McIntyre K, O'Shaughnessy J, Schwartzberg L, et al. Phase 2 study of eribulin mesylate as first-line therapy for locally recurrent or metastatic human epidermal growth factor receptor 2-negative breast cancer. Breast Cancer Res Treat. 2014;146:321-8.

28. Momtaz P, Park V, Panageas KS, et al. Safety of Infusing Ipilimumab Over 30 Minutes. J Clin Oncol. 2015;33:3454-8.

29. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clinical Cancer Res. 2013;19(14):3936-43.

30. Nomura M, Otsuka A, Kondo T, et al. Efficacy and safety of retreatment with nivolumab in metastatic melanoma patients previously treated with nivolumab. Cancer Chemother Pharmacol. 2017;80:999-1004.

31. Overman MJ, McDermott R,Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. 2017;18:1182-91.

32. Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol. 2018;19:51-64.

33. Payne R, Glenn L, Hoen H, et al. Durable responses and reversible toxicity of high-dose interleukin-2 treatment of melanoma and renal cancer in a Community Hospital Biotherapy Program. J Immunother Cancer. 2014;2:13.

34. Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2016;34:2969-79.

35. Rizvi N, Antonia S, Callahan MK, et al. Impact of tumor mutation burden on the efficacy of nivolumab or nivolumab + ipilimumab in small cell lung cancer: an exploratory analysis of CheckMate 032 (Abstract 11063). Presented at the International Association for the Study of Lung Cancer 18th World Conference on Lung Cancer, 15-18 October 2017, Yokohama, Japan.

36. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372:320-30.

37. Rugo HS, Delord JP, Im SA, et al. Safety and Antitumor Activity of Pembrolizumab in Patients with Estrogen Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer. Clinical Cancer Research. 2018;24(12):2804-11.

38. Schmid P, Cruz C, Braiteh F, et al. Atezolizumab in metastatic TNBC (mTNBC): long-term clinical outcomes and biomarker analyses. Cancer Res. 2017;77(13 Suppl):Abstract 2986 Presented at the 2017 annual meeting of the American Association for Cancer Research, 1-5 April 2017. Washington, DC.

39. Scott M, Ratcliffe MJ, Sharpe A, et al. Concordance of tumor and immune cell staining with Ventana SP142, Ventana SP263, Dako 28-8 and Dako 22C3 PD-L1 tests in NSCLC patient samples. DOI: 10.1200/JCO.2017.35.7_suppl.7 Journal of Clinical Oncology 35, no. 7_suppl (March 1 2017) 7-7.

40. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol. 2012;30:2055-62.

41. Topalian S, Hodi F, Brahmer J, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443–2454.

42. Tsao MS, Kerr KM, Kockx M, et al. PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project. J Thorac Oncol. 2018;13(9):1302-11. doi: 10.1016/j.jtho.2018.05.013.

43. Twelves C, Cortes J, Vahdat L, et al. Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies. Breast Cancer Res Treat. 2014;148(3):553-61.

44. Wainberg ZA, Hochster HS, George B, et al. Phase I study of nivolumab (nivo) + nab-paclitaxel (nab-P) ± gemcitabine (Gem) in solid tumors: Interim results from the pancreatic cancer (PC) cohorts. J Clin Oncol. 2017;35: 412-412.

45. Weber JS, Kudchadkar RR, Yu B, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. J Clin Oncol. 2013;31:4311-8.

46. Wong MKK, Morse MA, McDermott DF, et al. Overall survival of metastatic melanoma patients treated with HD IL-2 followed by immune checkpoint blockade of the CTLA-4 or the PD-1 pathways: analysis of data on the current use of HD IL-2. J Immunother Cancer. 2015;3(Suppl 2):P359.

47. Zídek Z, Anzenbacher P, Kmoníčková E. Current status and challenges of cytokine pharmacology. Br J Pharmacol. 2009;157:342–61.

APPENDIX 1: CLINICAL LABORATORY TESTS

Descriptions of the laboratory tests performed in this study are provided in the following appendices:

- Appendix 1A: Laboratory Tests Performed in This Study
- Appendix 1B: Local Clinical Laboratory Tests Obtained Prior to Study Drug Administration

Appendix 1A: Laboratory Tests Performed in This Study

<table>
<tr><th colspan="4">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Chemistry</th><th colspan="2">Serology</th></tr>
<tr><td rowspan="5">• 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="5">• 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 colspan="2">• Hepatitis B surface antigen (HBsAg)
• Hepatitis C virus antibody (anti-HCV)
• Human immunodeficiency virus (HIV) antibody</td></tr>
<tr><td colspan="2">Additional Labs</td></tr>
<tr><td colspan="2">• Creatine kinase
• Thyroid stimulating hormone (TSH)
• Free thyroxine (T4)
• Free or total triiodothyronine (T3)
• Lipase
• Amylase
• Serum or urine pregnancy (HCG)</td></tr>
<tr><td colspan="2">Coagulation</td></tr>
<tr><td colspan="2">• Partial thromboplastin time (PTT)
• Prothrombin time (PT)</td></tr>
<tr><th colspan="4">Urinalysis</th></tr>
<tr><td colspan="2">• Specific gravity
• pH
• Glucose
• Protein
• Bilirubin
• Ketones
• Leukocyte esterase
• Blood</td><td colspan="2">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.

Appendix 1B: Local Clinical Laboratory Tests Obtained Prior to Study Drug Administration

Chemistry		
• AST (SGOT) • ALT (SGPT) • Serum Creatinine • Blood urea nitrogen (BUN)	• Total bilirubin • Sodium • Potassium	• Pregnancy test (for WOCBP) • Any additional clinically-relevant test related to individual patient monitoring

Laboratory tests must be assessed by a local laboratory within 24 hours prior to study drug administration in each cycle, or as soon as locally feasible.

APPENDIX 2: SCHEDULE OF ELECTROCARDIOGRAM, VITAL SIGNS, PHARMACOKINETICS, [redacted], AND IMMUNOGENICITY SAMPLE ASSESSMENTS

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	EOT & Follow-up
Predose		VS	VS[c]	VS[c] (once)	VS[c] (once)	VS[c] (once)	VS	VS[c] (once)	VS	VS[c]	VS[c] (EOT only)
		ECG	ECG[d] + PK-214				PK-214		PK-214		
			PK-nivo						PK-nivo (only Cycles 3, 8, 16, 24, 36)		
			[redacted]			[redacted]			[redacted]	[redacted]	[redacted]
			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 only)
			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		

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

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	EOT & Follow-up
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		
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			ECGd + 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]					

Abbreviations: [redacted]; ECG = electrocardiogram; IG-214 = immunogenicity samples for NKTR-214; IG-nivo = immunogenicity samples for nivolumab; 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; SOI = Start of NKTR-214 infusion; VS = vital signs

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 visits where study drug is not being administered (i.e., Cycle 1 on Days 2, 3, 8 and Cycle 2 Day 8, and at EOT). Beginning with Cycle 3 and beyond, vital signs on Day 8 should be collected according to the Investigator's discretion based on the clinical status of the patient.

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.

[redacted]

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 - NKTR-214 will be administered IV over 30 (± 5) minutes at a starting dose of 0.006 mg/kg every 3 weeks (± 3 days). Nivolumab administration should start at least 30 minutes from the end of NKTR-214 administration. The time tracking in the above table assumes that the nivolumab infusion starts 30 minutes after the end of NKTR-214 infusion.

[redacted]

Appendix 2 Table 2: Parts 3/4, Cohort A (Concurrent Dosing)

- **Schedule 1: Concurrent Dosing NKTR-214 0.006 mg/kg q3w + Nivo 360mg flat dose + Ipi 1 mg/kg q6w**
- **Schedule 2: Concurrent Dosing NKTR-214 0.006 mg/kg q3w + Nivo 1 mg/kg × 4 doses + ipi 3 mg/kg q3w × 4 doses (**then NKTR-214 0.006 mg/kg q3w + Nivo 360 mg q3w maintenance**)**
- **Schedule 3: Concurrent Dosing NKTR-214 0.006 mg/kg q3w + Nivo 3 mg/kg × 4 doses + ipi 1 mg/kg q3w × 4 doses (**then NKTR-214 0.006 mg/kg q3w + Nivo 360 mg q3w maintenance**)**

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 11	Day 1[b]	Day 3	Day 8	Day 1[b]	Day 8	EOT & Follow-up
Predose	VS	VS	VS[c] (q1h x4) for Part 3; VS[c] (once) for Part 4	VS[c] (q1h x2) for Part 3; VS[c] (once) for Part 4	VS[c] (once)	VS[c] (once) for Part 3 only	VS		VS[c] (once)	VS	VS[c]	VS[c] (EOT only)
	ECG	ECG[d] + PK-214					PK-214			PK-214		
		PK-nivo					PK-nivo			PK-nivo (Cycles 3, 5, 7, 9, 13, 17,23,35)		
		PK-ipi					PK-ipi (Schedules 2&3 only)			PK-ipi[h] Schedule 1: Cycles 3, 5, 7, 9, 13, 17, 23, 35 Schedules 2&3: Cycles 3, 4, 5 and 7 only		

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 11	Day 1[b]	Day 3	Day 8	Day 1[b]	Day 8	EOT & Follow-up
Predose, Cont.		[redacted]			[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	
		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			IG-nivo (Cycles 3, 5, 7, 9, 13, 17)		
		IG-ipi					IG-ipi			IG-ipi Schedule 1: Cycles 3, 5, 7, 9, 13, 17, 23, 35 Schedules 2&3: Cycles 3, 5, 7, 9 and 13		

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 11	Day 1[b]	Day 3	Day 8	Day 1[b]	Day 8	EOT & Follow-up
T=0:00 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		
T=01:00 - 01:30[g]	Nivo Infusion[g]		Nivo Infusion					Nivo Infusion			Nivo Infusion		
T=01:30 - 02:00	End of nivo infusion		PK-nivo										
T=02:00 - 02:30[i]	Ipilimumab (Ipi) infusion[i]		Ipi infusion					Ipi infusion (Schedules 2&3 only)			Ipi infusion Schedule 1: only on cycles Ipi is given Schedules 2&3: Cycles 3 and 4 only		
T=02:30 – 03:00	End of Ipi infusion		PK-ipi										
T=03:00 (± 30 min) SOI			ECG[d] +PK-214[f]					PK-214					

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 11	Day 1[b]	Day 3	Day 8	Day 1[b]	Day 8	EOT & Follow-up
T=03:00-04:00 SOI or 1 hr following the end of the last study drug infusion (whether nivo or ipi)		VS					VS			VS		
T=04:00-05:00 SOI or 2 hrs following the end of the last study drug infusion (whether nivo or ipi)		VS										
T=05:00-06:00 SOI or 3 hrs following the end of the last study drug infusion (whether nivo or ipi)		VS										
T=06:00 + 2 hrs SOI		ECG[d] +PK-214[f]					PK-214					
T=48:00 ± 4 hrs SOI				ECG[d] + PK-214[f]				PK-214				
T=168:00 ± 4 hrs SOI					ECG[d] + PK-214[f]				PK-214			

Footnotes and abbreviations appear at the end of Appendix 2

Appendix 2 Table 2: Parts 3/4, Cohort B (Staggered Dosing of Ipilimumab)

- **Schedule 1: Staggered Dosing NKTR-214 0.006 mg/kg q3w + Nivo 360mg flat dose + Ipi 1 mg/kg q6w**
- **Schedule 2: Staggered Dosing NKTR-214 0.006 mg/kg q3w + Nivo 1 mg/kg × 4 doses + ipi 3 mg/kg q3w × 4 doses (**then NKTR-214 0.006 mg/kg q3w + Nivo 360 mg q3w maintenance**)**
- **Schedule 3: Staggered Dosing NKTR-214 0.006 mg/kg q3w + Nivo 3 mg/kg × 4 doses + ipi 1 mg/kg q3w × 4 doses (**then NKTR-214 0.006 mg/kg q3w + Nivo 360 mg q3w maintenance**)**

	Screening[a]	Cycle 1					Cycle 2		Cycle 3[j]			Cycle 4 and Beyond[k]		Post Treatment
Event	Day -28 to -1	Day 1[b]	Day 2	Day 3	Day 8	Day 11	Day 1[b]	Day 8	Day 1[b]	Day 3	Day 8	Day 1[b]	Day 8	EOT & Follow-up
Predose	VS	VS	VS[c] (q1h x4) for Part 3; VS (once) for Part 4	VS[c] (q1h x2) for Part 3; VS (once) for Part 4	VS[c] (once)	VS[c] (once) for Part 3 only	VS	VS[c] (once)	VS		VS[c]	VS	VS[c]	VS[c] (EOT only)
	ECG	ECG[d] + PK-214					PK-214		PK-214			PK-214		
		PK-nivo							PK-nivo			PK-nivo (Cycles 5, 7, 9, 13, 17, 23, 35)		
									PK-ipi[h]			PK-ipi[h] Schedule 1: Cycles 5, 7, 9, 13, 17, 23, 35 Schedules 2&3: Cycles 4, 5, 6, 7, 9		

Event		Screening[a]	Cycle 1					Cycle 2		Cycle 3[j]			Cycle 4 and Beyond[k]		Post Treatment
		Day -28 to -1	Day 1[b]	Day 2	Day 3	Day 8	Day 11	Day 1[b]	Day 8	Day 1[b]	Day 3	Day 8	Day 1[b]	Day 8	EOT & Follow-up
Predose, Cont.			[redacted]			[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
			IG-214					IG-214		IG-214			IG-214 (only on odd-number cycles – Cycles 5, 7, 9, etc.)		IG-214 (EOT and at the first 3-month follow-up visit)
			IG-nivo					IG-nivo		IG-nivo			IG-nivo (Cycles 5, 7, 9, 13, 17, 23, 35)		
			IG-Ipi					IG-Ipi		IG-Ipi			IG-Ipi Schedule 1: Cycles 5, 7, 9, 13, 17, 23, 35 Schedules 2&3: Cycles 4, 5, 6, 7, 9		
T=0:00 hr	Start of 30 min NKTR-214 Infusion (SOI)		214 Infusion					214 Infusion		214 Infusion			214 Infusion		

Event		Screening[a]	Cycle 1					Cycle 2		Cycle 3[j]			Cycle 4 and Beyond[k]		Post Treatment
		Day -28 to -1	Day 1[b]	Day 2	Day 3	Day 8	Day 11	Day 1[b]	Day 8	Day 1[b]	Day 3	Day 8	Day 1[b]	Day 8	EOT & Follow-up
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			PK-214		
T=01:00 - 01:30[g]	Nivo Infusion[g]		Nivo Infusion					Nivo Infusion		Nivo Infusion			Nivo Infusion		
T=01:30 - 02:00	End of nivo infusion		PK-nivo												
T=02:00 - 02:30[i]	Ipilimumab (Ipi) infusion[i]									Ipi infusion Schedule 1: only on cycles Ipi is given Schedules 2&3: Cycles 4, 5, 6			Ipi infusion Schedule 1: only on cycles Ipi is given Schedules 2&3: Cycles 4, 5, 6		
T=02:30 – 03:00	End of Ipi infusion									PK-ipi[h]					
T=03:00 (± 30 min) SOI			ECG[d] +PK-214[f]							PK-214					

Event	Screening[a]	Cycle 1					Cycle 2		Cycle 3[j]			Cycle 4 and Beyond[k]		Post Treatment
	Day -28 to -1	Day 1[b]	Day 2	Day 3	Day 8	Day 11	Day 1[b]	Day 8	Day 1[b]	Day 3	Day 8	Day 1[b]	Day 8	EOT & Follow-up
T=03:00-04:00 SOI or 1 hr following the end of the last study drug infusion (whether nivo or ipi)		VS					VS		VS			VS		
T=04:00-05:00 SOI or 2 hrs hr following the end of the last study drug infusion (whether nivo or ipi) - (for Part 3 only)		VS												
T=05:00-06:00 SOI or 3 hrs hr following the end of the last study drug infusion (whether nivo or ipi) - (for Part 3 only)		VS												
T=06:00 + 2 hrs SOI		ECG[d] + PK-214[f]							PK-214					
T=48:00 ± 4 hrs SOI				ECG[d] + PK-214[f]						PK-214				
T=168:00 ± 4 hrs SOI					ECG[d] + PK-214[f]						PK-214			

Abbreviations: [redacted]; ECG = electrocardiogram; IG-214 = immunogenicity samples for NKTR-214; IG-nivo = immunogenicity samples for nivolumab; IG-ipi = immunogenicity samples for ipilimumab; Ipi = Ipilimumab; Nivo = Nivolumab; PK-214 = blood samples for pharmacokinetic (PK) analyses of NKTR-214 and its metabolites; PK-ipi = blood samples for PK analyses of ipilimumab; PK-nivo = blood samples for PK analyses of nivolumab; SOI = Start of NKTR-214 infusion; VS = vital signs;

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 visits where study drug is not being administered (i.e., Cycle 1 on Days 2, 3, 8, 11, Cycle 2 Day 8, and at EOT. Beginning with Cycle 3 and beyond, vital signs on Day 8 should be collected according to the Investigator's discretion based on the clinical status of the patient.

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.

[redacted]

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 - NKTR-214 will be administered IV over 30 (± 5) minutes at a starting dose of 0.006 mg/kg every 3 weeks (± 3 days). Nivolumab administration should start at least 30 minutes from the end of NKTR-214 administration. The time tracking in the above table assumes that the nivolumab infusion starts 30 minutes after the end of NKTR-214 infusion.

h. PK-ipi – Ipilimumab PK Sampling for Cohort B may be adjusted based on the Cycle ipilimumab is added.

i. Ipi Infusion - Ipilimumab will be continuously dosed q6w or only for 4 doses based on assigned dosing schedule. NKTR-214 will be administered IV over 30 (± 5) minutes at a starting dose of 0.006 mg/kg every 3 weeks (± 3 days). Nivolumab administration should start at least 30 minutes from the end of NKTR-214 administration. Ipilimumab will be administered at least 30 minutes after completion of nivolumab infusion. The time tracking in the above tables assumes that the nivolumab infusion starts 30 minutes after the end of the NKTR-214 infusion and the ipilimumab infusion starts 30 minutes after the end of the nivolumab infusion.

j. Cycle 3 or cycle in which ipilimumab will be added to NKTR-214 and nivolumab.

k. Cycle 4 or the first cycle following addition of ipilimumab.

APPENDIX 3: CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM

Table 26 provides a management algorithm for possible signs of CVA and follow-up of CVA. This general guideline constitutes guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor.

Table 26: Cerebrovascular Accident Adverse Event Management Algorithm

CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM **This guideline pertains to all patients in the doublet or triplet immunotherapy cohorts.**	
For unexplained neurological symptoms (such as hemiparesis, confusion, dysarthria, or visual disturbances) that may be associated with CVA: **perform neurological imaging with MRI including diffusion-weighted imaging (DWI) as soon as feasible after initial presentation of symptoms, preferably within 24 hours** (DWI MRI is preferred, but if contraindicated, alternative imaging modalities may be used). If imaging is consistent with a CVA, proceed to the following:	
1	For any new CVA events confirmed by imaging (DWI MRI is preferred, unless contraindicated), regardless of neurological symptoms (e.g., cryptogenic CVA): • Discontinue study treatment for patients receiving doublet and triplet immunotherapy For suspected TIA without clear alternative etiology: • Discontinue study treatment for patients receiving triplet immunotherapy • Study treatment for patients receiving doublet immunotherapy may be continued only after careful risk-benefit assessment by the Investigator
2	Obtain a neurology consultation
3	Perform laboratory assessments (complete blood count [CBC] with differential, serum blood urea nitrogen [BUN], and creatinine)
4	Consider cardiac echocardiogram (trans-esophageal as appropriate) to evaluate for potential source of emboli

Abbreviations: CVA = cerebrovascular accident; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging; TIA = transient ischemic attack.