Nektar Therapeutics

CLINICAL STUDY PROTOCOL

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

Protocol Number: 16-214-05

Protocol Date Final: 23 December 2020

Protocol Version No. Amendment 7.0

Supersedes: Amendment 6.0 dated 10 February 2020
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Sponsor: Nektar Therapeutics
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CONFIDENTIALITY STATEMENT

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INVESTIGATOR SIGNATURE PAGE

Nektar Therapeutics

TITLE:	A Phase 1/2, Open-label, Multicenter Study to Investigate the Safety and Preliminary Efficacy of Combined Bempegaldesleukin (NKTR-214) and Pembrolizumab with or without Chemotherapy in Patients with Locally Advanced or Metastatic Solid Tumors
PROTOCOL NUMBER:	16-214-05
PHASE OF STUDY:	Phase 1/2
PROTOCOL DATE:	23 December 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 to Investigate the Safety and Preliminary Efficacy of Combined Bempegaldesleukin (NKTR-214) and Pembrolizumab with or without Chemotherapy in Patients with Locally Advanced or Metastatic Solid Tumors

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Signing Reason: I approve this document
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ABBREVIATIONS

Abbreviation or Term	Definition
1L	first line
2L	second line
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the curve
BICR	blinded independent central review
BMI	body mass index
BOR	best overall response
BUN	blood urea nitrogen
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CL	Clearance
C_{max}	maximum concentration
CNS	central nervous system
CPS	Combined Positive Score
CR	complete response
CLcr	creatinine clearance
CRS	Cytokine Release Syndrome
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

Abbreviation or Term	Definition
DCI	data collection instrument
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOAC	direct oral anticoagulation
DOR	duration of response
DVT	deep vein thrombosis
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
EOI	End of Infusion
EOT	End of Treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCT	Hematocrit
HCV	hepatitis C virus
Hgb	Hemoglobin
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
Hr	hour(s)
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviation or Term	Definition
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
INR	international normalized ratio
IRB	Institutional Review Board
IV	Intravenous
Kg	Kilogram
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
LVEF	left ventricular ejection fraction
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	minute(s)
Mg	Milligram
mL	Milliliter
mmHg	millimeters of mercury
Mo	month
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
N1	sample size at Stage 1
N2	sample size at Stage 2
NCI	National Cancer Institute
NE	Inevaluable
NK	natural killer
NKTR-214, bempeg, BEMPEG	bempegaldesleukin (International Nonproprietary Name [INN] for NKTR-214)

Abbreviation or Term	Definition
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PE	pulmonary embolism
PEG	polyethylene glycol
PFS	progression-free survival
PK	Pharmacokinetic
po	Orally
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
q1h x 2	every hour for 2 hours
q1h x 3	every hour for 3 hours
q1h x 4	every hour for 4 hours
q1w	every week
q2w	every 2 weeks
q3w	every 3 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
ROS1	c-ros oncogene 1
RP2D	recommended Phase 2 dose
SAE	serious adverse event

Abbreviation or Term	Definition
SAP	statistical analysis plan
SD	stable disease
SLD	sum of the longest diameters
SOP	standard operating procedure
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
SWFI	sterile water for injection
$t_{1/2}$	half-life
T3	Triiodothyronine
T4	free thyroxine
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TIL	tumor infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
TP	total protein
TPS	tumor proportion score
Treg	regulatory T cell
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
USP	United States Pharmacopeia
V_d	volume of distribution
WBC	white blood cell
WCBP	women of childbearing potential

1.0 STUDY SYNOPSIS

Name of Sponsor:	Nektar Therapeutics
Name of Finished Products:	Bempegaldesleukin (NKTR-214) Drug Product Keytruda®
Name of Active Ingredients:	Bempegaldesleukin (NKTR-214) Drug Substance Pembrolizumab (anti-PD-1)
Title of Study:	A Phase 1/2, Open-label, Multicenter Study to Investigate the Safety and Preliminary Efficacy of Combined Bempegaldesleukin (NKTR-214) and Pembrolizumab with or without Chemotherapy in Patients with Locally Advanced or Metastatic Solid Tumors
Duration of Treatment:	Patients will be treated until disease progression, death, unacceptable toxicity, symptomatic deterioration, lost to follow up, the Investigator decides to discontinue treatment, the patient decides to discontinue treatment or withdraw consent 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:	**Primary Objectives: Dose Optimization or Dose Expansion Cohorts** The primary objectives in the dose optimization cohorts are: • To evaluate the safety and tolerability of NKTR-214 in combination with pembrolizumab. • To define the MTD/RP2D and optimal dosing schedule of NKTR-214 in combination with pembrolizumab. The primary objective in all the dose expansion cohorts is: • To determine the ORR per blinded independent central review (BICR) by RECIST 1.1 of NKTR-214 plus pembrolizumab with or without systemic chemotherapy in patients with untreated metastatic NSCLC. **Secondary Objectives: Dose Optimization and/or Dose Expansion Cohorts** The secondary objectives in the dose optimization and/or dose expansion cohorts are: • To evaluate safety and tolerability of NKTR-214 plus pembrolizumab with or without systemic chemotherapy in patients with untreated NSCLC (dose expansion only). • To assess the preliminary efficacy (per BICR) of NKTR-214 plus pembrolizumab with or without systemic chemotherapy: – objective response rate (ORR) by RECIST 1.1 (dose optimization only) – duration of response (DOR) by RECIST 1.1 – clinical benefit rate (CBR) by RECIST 1.1 – time to response (TTR) by RECIST 1.1

	– progression-free survival (PFS) by RECIST 1.1 – overall survival (OS) [redacted]
Study Population	Adults aged 18 years and older with locally advanced or metastatic solid tumors.
Number of Patients (planned):	Thirty-five patients were enrolled in the original protocol and amendments (up to and including Amendment 4). Additionally, 66 patients were enrolled in the dose expansion cohort under Amendments 5 and 6. A total of 13 patients have been enrolled in the dose optimization cohort under Amendments 5 and 6. With this amendment the following number of patients will be enrolled: Dose Optimization Cohorts (Cohorts 1a and 1b): A total of approximately 40 patients will be enrolled. Dose Expansion Cohorts 2 and 3: Approximately 58 response-evaluable patients may be enrolled into each cohort. Patients who are not response-evaluable may be replaced. Up to 100 patients may be enrolled in each cohort to reach the number of response-evaluable patients. Dose Expansion Cohorts 4 and 5: Approximately 63 response-evaluable patients may be enrolled into each cohort. Patients who are not response-evaluable may be replaced. Up to 100 patients may be enrolled in each cohort to reach the number of response-evaluable patients.
Number of Study Sites:	Approximately 50 sites; dose optimization will be conducted at select sites in the USA.
Countries:	Dose Optimization Cohorts: at select sites in the USA Dose Expansion Cohorts: USA, Europe, and Australia; additional countries may be added
Study Design:	This is a Phase 1/2, open-label, multicenter, study of NKTR-214 in combination with pembrolizumab with or without systemic chemotherapy in patients with metastatic solid tumors. The dose optimization cohorts (Cohorts 1a and 1b) will include first- and second-line (1L and 2L) melanoma, non-small cell lung cancer (NSCLC), urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), and hepatocellular carcinoma (HCC). The dose optimization Cohort 1a will include

	patients enrolled in the 3 + 3 dose optimization cohort and the dose optimization Cohort 1b will include patients enrolled in the step-up dose optimization cohort. The dose expansion cohorts will include first-line NSCLC patients (Cohorts 2, 3, 4, and 5). The original protocol and amendments (up to and including Amendment 4), evaluated atezolizumab in combination with NKTR-214 (0.006 mg/kg) for treatment of second-line NSCLC and first- and second- line urothelial carcinoma and pembrolizumab in combination with NKTR-214 (0.006 mg/kg) for treatment of first-line metastatic melanoma and first- and second-line NSCLC. Patients in the pembrolizumab first-line NSCLC cohort will continue on study in the dose expansion cohort of Amendment 5.0 or subsequent versions; however, the atezolizumab second-line NSCLC and first- or second-line urothelial carcinoma cohorts and the pembrolizumab first-line melanoma cohort have been closed to further enrollment. Patients on study who were enrolled in these cohorts under prior amendments will continue treatment as described in Amendment 5.0 and subsequent versions. Patients will be followed for efficacy and safety until the patient is lost to follow-up, withdraws consent, or patient death. Based on the findings from the NKTR-214 monotherapy study (EXCEL; 15-214-01) (see Section 2.1.4.1) and findings from the dose-escalation part of the PIVOT-02 study (16-214-02) (see Section 2.1.4.2), the RP2D of NKTR-214 in combination with nivolumab 360 mg q3w was determined to be 0.006 mg/kg. **Dose Optimization Cohorts (Cohorts 1a and 1b)** Patients enrolled in the 3 + 3 dose optimization schema (Cohort 1a) will start NKTR-214 at a dose of 0.008 mg/kg q3w with pembrolizumab. Patients enrolled in the step-up dose optimization schema (Cohort 1b) will start NKTR-214 q3w with pembrolizumab at the previously tolerated dose established in the 3 + 3 dose optimization schema as determined by the SRC. Doses will be increased in 0.002 mg/kg increments for the dose optimization cohorts (Figure 2). At the Investigator's discretion, step-up dose increases may be delayed by 1 cycle. Moreover, the SRC or Sponsor may determine that inadequate information has been obtained in a cohort of 3 patients and may enroll additional patients to further assess the benefit/risk profile at a given dose level. For dose optimization cohorts, the SRC will decide the following: o Dose escalation to the next dose level. o 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. o Decision to evaluate NKTR-214 in combination with pembrolizumab at higher doses and different dose schedules to assess the benefit/risk profile within the anticipated total number of 40 patients. The dose-limiting toxicity (DLT) evaluation period for the 3 + 3 and step-up dose optimization cohorts will be 3 weeks (21 days) (Table 9). Any DLT past the DLT window is a delayed DLT. **Dose Expansion Cohorts (Cohorts 2, 3, 4, and 5)** **Dose Expansion Cohort 2 (0.006 mg/kg of NKTR-214)** The Dose Expansion Cohort 2 is currently enrolling first-line NSCLC patients at a dose of 0.006 mg/kg of NKTR-214 combined with pembrolizumab. **Dose Expansion Cohort 3 (0.010 mg/kg of NKTR-214)** Following review of safety and efficacy data from Cohort 2, approximately 58 response-evaluable first-line NSCLC patients may be enrolled in Cohort 3, starting at a dose of 0.010 mg/kg of NKTR-214 combined with pembrolizumab. Following data review for safety and efficacy, dose adjustments may be made for subsequent patients within Cohort 3 in accordance with the findings from the dose

	optimization cohorts. Enrollment may be stopped before 58 response-evaluable patients are enrolled. **Dose Expansion Cohorts 4 and 5** Following review of safety and efficacy data from Cohorts 2 and 3, a decision may be made on whether to initiate Cohorts 4 and 5. Approximately 63 response-evaluable, first-line, nonsquamous NSCLC patients may be enrolled in Cohort 4, starting at a dose of either 0.006 mg/kg or 0.010 mg/kg of NKTR-214 (depending on available data from Cohorts 2 and 3) combined with pembrolizumab and platinum-based chemotherapy. Following data review for safety and efficacy, dose adjustments may be made for subsequent patients within Cohort 4 or Cohort 5 in accordance with the findings from the dose expansion cohorts.

Key Eligibility Criteria:	o Provide written, informed consent to participate in the study and follow the study procedures.
	o Age 18 years or older at the time of signing the informed consent form (ICF).
	o Life expectancy > 12 weeks from the time of enrollment as determined by the Investigator.
	o In the dose optimization cohorts, patients may have received no more than 1 prior line of systemic therapy for metastatic cancer. 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 in a non-palliative setting and is stopped for progression of disease.
	o Patients must have a minimum of 6 months of response to any non-palliative cancer-directed treatment.
	o Prior IL-2 therapy is allowed for patients in the dose optimization cohorts who have completed therapy, and who have reported no severe ADRs or had all ADRs completely resolved. Prior IL-2 therapy is not allowed for patients in the dose expansion cohorts.
	o Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
	o Measurable disease per RECIST 1.1.
	o A documented left ventricular ejection fraction (LVEF) > 45% using standard echocardiogram (ECHO) or multigated acquisition (MUGA) scan within 90 days prior to Cycle 1 Day 1
	o Oxygen saturation ≥ 90% on room air for all indications.
	o Patients with hypertension must be on ≤ 2 antihypertensive medications and without change for the 14 days prior to randomization. Screening blood pressure must be systolic < 150 mm Hg and < 90 mm Hg for diastolic blood pressure.
	  o For France only: screening blood pressure must be systolic < 140 mm Hg and < 90 mm Hg for diastolic blood pressure.
	o A brain magnetic resonance image (MRI) at Screening is required for all patients with metastatic NSCLC, and for patients with other tumor types who have known brain metastasis.
	o Patients with brain metastases are eligible if all the criteria below are fulfilled:
	  a. Brain metastases must be treated at least 2 weeks prior to study treatment initiation.
	  b. Brain imaging after treatment and within the screening period must demonstrate no new or progressing brain metastases.
	  c. No requirement for systemic corticosteroids >10 mg/day prednisone equivalents at therapy initiation. Stable doses of anticonvulsants are allowed.
	  d. No clinically significant symptoms associated with brain metastases.

- Tumor tissue sample is required for all patients. Acceptable samples include archival tissue obtained no more than 12 months prior to enrollment if the patient has not received systemic treatment between the time of biopsy/resection and enrollment. Otherwise, a fresh tumor biopsy taken during screening is required.
- For France only: enrolled patients must be affiliated to a Social Security System.

The following additional inclusion criteria are for the dose optimization cohorts (see Section 4.1.1) or dose expansion cohort (see Section 4.1.2).

Dose Optimization Cohorts (Cohorts 1a and 1b)

Tumor Types Included in Dose Optimization Cohorts

(NKTR-214 and Pembrolizumab)

Tumor Type	Line of Treatment in Metastatic Setting	PD-L1 Status
Melanoma	1st and 2nd	Any
Non-small cell lung cancer	1st and 2nd	Any
Urothelial carcinoma	1st and 2nd	Any
Head and neck squamous cell carcinoma	1st and 2nd	Any
Hepatocellular carcinoma	1st and 2nd	Any

1L and 2L Melanoma

- Histologically confirmed Stage IV (metastatic) melanoma.

1L and 2L Non-small Cell Lung Cancer

- Histologically confirmed diagnosis of Stage IV NSCLC.
- Patients with actionable mutations with approved targeted therapy in NSCLC are excluded. Testing for mutations should be performed per standard of care.

1L and 2L Urothelial Carcinoma

- Histologically confirmed diagnosis of metastatic urothelial carcinoma.

1L and 2L Head and Neck Squamous Cell Carcinoma (HNSCC)

- Histologically confirmed diagnosis of metastatic HNSCC.

1L and 2L Hepatocellular Carcinoma (HCC)

- Histologically confirmed diagnosis of metastatic HCC.

Dose Expansion Cohorts

1L Non- Small Cell Lung Cancer (Cohorts 2, 3, 4, and 5)

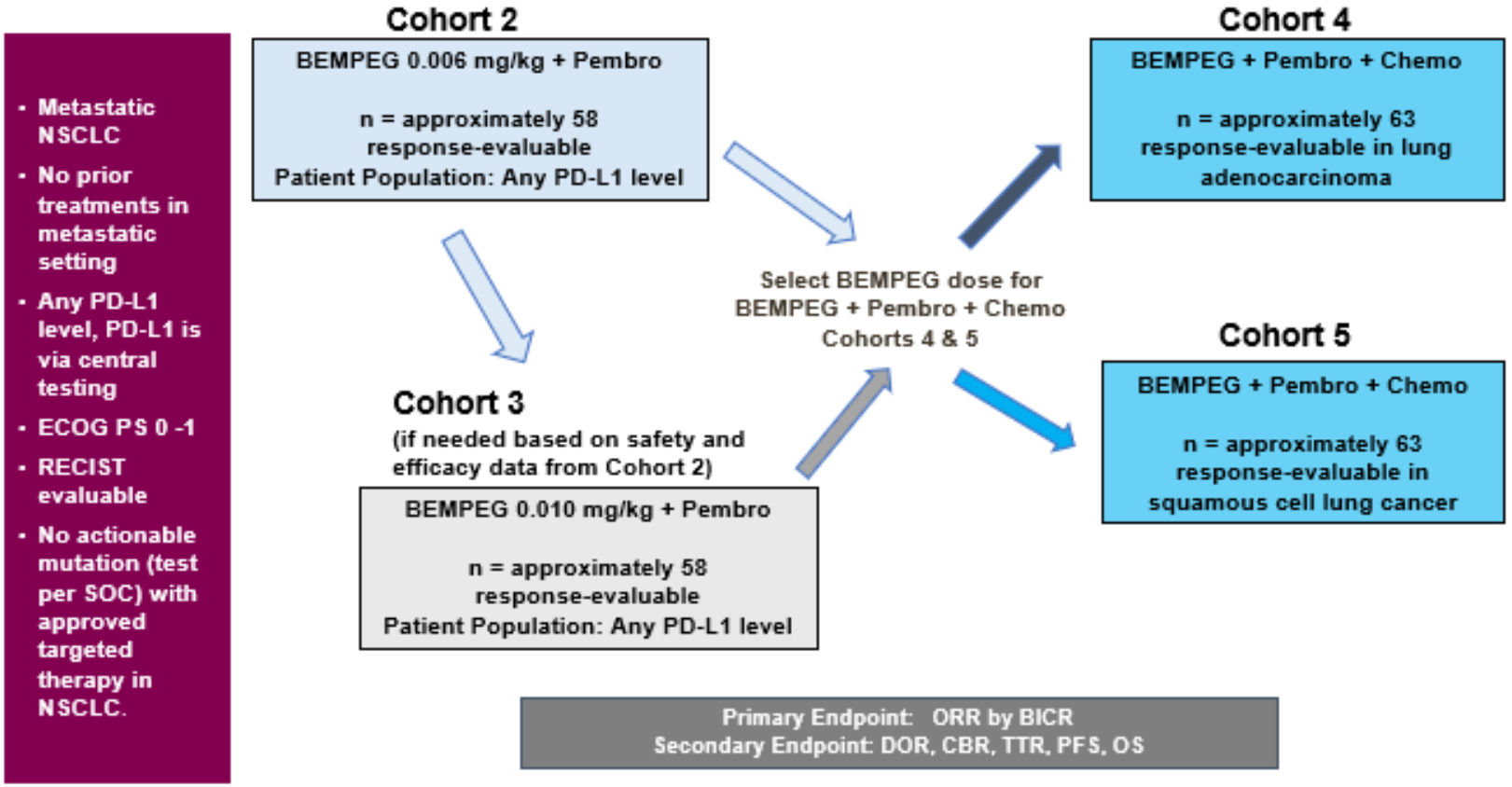
- Histologically confirmed diagnosis of Stage IV NSCLC.

	○ Tumor tissue sample is required to be submitted to the central lab for all patients prior to enrollment. Acceptable samples include archival tissue obtained no more than 12 months prior to enrollment if the patient has not received systemic treatment between the time of biopsy/resection and enrollment. Otherwise, a fresh tumor biopsy taken during screening is required. A tracking number confirming shipment of the sample to the central laboratory must be supplied prior to Cycle 1 Day 1. Within each subgroup, this is: ○ PD-L1 negative (PD-L1 < 1%; Cohort 2.1): 20 response-evaluable patients ○ PD-L1 low/intermediate (PD-L1 1% to 49%; Cohort 2.2): 18 response-evaluable patients ○ PD-L1 highly positive (PD-L1 ≥ 50%; Cohort 2.3): 20 response-evaluable patients ○ For France only: patients in subgroup PD-L1 < 50% (Cohorts 2.1, 2.2) will be excluded. Eligibility for PD-L1 status can be determined with a local or central PD-L1 test. ○ If the decision is made to open Cohort 3, approximately 58 response-evaluable patients may be enrolled. ○ If the decision is made to open Cohorts 4 and 5, approximately 63 response-evaluable patients may be enrolled in each cohort. ○ Patients with actionable mutations with approved targeted therapy in NSCLC are excluded. Testing for mutations should be performed per standard of care. ○ Must not have received anti-cancer therapy for treatment of metastatic lung cancer. ○ Must not have received prior immunotherapy.
Test Product, Dose and Mode of Administration:	Each patient's NKTR-214 dose will be determined by the NKTR-214 dose optimization or dose expansion schema and the patient's weight in kilograms (Section 5.3.2). The patient's weight in kilograms will be determined on Day 1 before the start of each cycle; for weight changes of ± 10% from baseline, recalculation of dose is not required. Patients enrolled on previous amendments will follow dosing schedule of the amendment they were consented to. Pembrolizumab will be dosed as per the Pharmacy Manual. **Dose Optimization Cohorts (Cohorts 1a and 1b)** **Study Drug Administration: 3 + 3 Dosing (Cohort 1a) Schema** ○ NKTR-214 will be administered IV over 30 (± 5) minutes at a starting dose of 0.008 mg/kg. Please refer to the Pharmacy Manual for additional details for study drug administration. **Study Drug Administration: Step-up Dosing (Cohort 1b) Schema** ○ NKTR-214 will be administered IV over 30 (± 5) minutes starting at the previously tolerated dose established in the 3 + 3 dosing schema as determined by the Safety Review Committee (SRC) for the step-up dosing schema. This dose may increase at each cycle for individual patients at increments of 0.002 mg/kg per the dose optimization schema in Figure 2. Please refer to the Pharmacy Manual for additional details for study drug administration. **Dose Expansion Cohorts** ○ Refer to the Pharmacy Manual for additional details related to study drug administration.

	○ Cohorts 4 and 5 may include: cisplatin, carboplatin, pemetrexed, nab-paclitaxel, and paclitaxel and will be dosed per local practice and label. ○ NKTR-214 will be administered q3w IV over 30 (± 5) minutes at the following doses: **Cohort 2** ○ Starting dose of NKTR-214: 0.006 mg/kg. **Cohort 3** ○ Starting dose of NKTR-214: 0.010 mg/kg. **Cohort 4** ○ Starting dose of NKTR-214: starting at a dose of either 0.006 mg/kg or 0.010 mg/kg of NKTR-214 (depending on available data from Cohorts 2 and 3). **Cohort 5** ○ Starting dose of NKTR-214: starting at a dose of either 0.006 mg/kg or 0.010 mg/kg of NKTR-214 (depending on available data from Cohorts 2 and 3).
Safety:	Safety will be assessed 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 • physical examination
Pharmacokinetics:	Blood samples for PK analyses will be collected from all patients at multiple scheduled sampling times. **Dose Optimization Cohorts (Cohorts 1a** and **1b)** For patients in 3 + 3 dose optimization cohort (Cohort 1a), blood for NKTR-214 PK determinations will be collected for Cycle 1 on Days 1, 3, 5, and 8 per the sampling scheme in Table 1. For Cycle 2 and every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc.), blood will be collected predose on Day 1. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing. For patients in the step-up dose optimization cohort (Cohort 1b), blood for NKTR-214 PK determinations will be collected for Cycle 1 and only the first cycle of subsequent cycle(s) in which the patient is administered a step-up dose on Days 1, 3, 5 and 8 per the sampling scheme in Table 1. With the exception of cycles in which the patient is administered a step-up dose, in Cycles ≥ 2, blood will be collected on predose on Day 1 on Cycle 2 and every 3 cycles after Cycle 2 (ie Cycles 5, 8, 11, etc.). For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing. **Dose Expansion Cohorts (Cohorts 2, 3, 4, and 5):** Blood for NKTR-214 PK determinations will be collected for Cycle 1 on Days 1, 3, 5, and 8 per the sampling scheme in Table 2. Blood will be collected predose on Day 1 of Cycle 2 and every 3 cycles after Cycle 2. Plasma concentrations of NKTR-214 and its metabolites will be measured for each PK sample using validated or qualified method(s). 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 ($t_{½}$) will be estimated from plasma concentration-time data where feasible.
Pharmacodynamics:	Systemic and tumor tissue-based pharmacodynamic effects of NKTR-214 in combination with pembrolizumab will be examined. Blood samples (C1D1) and tumor tissue samples (screening) will be collected from all patients prior to their first dose of NKTR-214. Blood samples for pharmacodynamic analyses will be collected from all patients enrolled in the dose

	optimization and expansion cohorts. Tumor tissue samples for pharmacodynamic analyses will be collected during combination treatment from all patients enrolled in the dose optimization cohorts. Blood samples will be assessed for markers of immune system activation, cytokines, immune cell populations, RNA analysis, genetic profiling and circulating tumor deoxyribonucleic acid (DNA). Tissue samples will be assessed for characterization of tumor infiltrating lymphocytes (TILs) and immune system- and cancer-related genes and proteins. [redacted]
Efficacy:	Tumor assessments will be performed every 9 weeks ± 7 days from Cycle 1 Day 1, at EOT, and at the 90-day long-term follow-up visits. If a patient does not experience PD per BICR by RECIST 1.1 when study drug treatment was discontinued, tumor assessments should continue every 90 (± 10) days until PD, consent withdrawal, start of new systemic therapy, death, or study termination by Sponsor. The primary efficacy measurement will be confirmed ORR in response-evaluable patients per BICR by RECIST 1.1 based on data provided by the investigator site. Other efficacy outcomes will include: • duration of response (DOR) • clinical benefit rate (CBR) • time to response (TTR) • progression-free survival (PFS) • overall survival (OS)
Statistical Methods:	**Safety:** Safety assessments will include AEs, local clinical laboratory tests, vital signs, and physical examinations. The incidence of dose-limiting toxicities (DLTs) will be evaluated for each dose optimization cohort. All treatment-emergent adverse events (TEAEs) will be summarized by system organ class and preferred term for each dose cohort. 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 cohort. All abnormal findings in clinical laboratory test results, vital signs, and physical examinations will be listed. **Efficacy:** All efficacy assessments, including ORR, BOR, TTR, DOR, CBR, and PFS, will be based on RECIST 1.1. ORR based on BICR will be the primary efficacy endpoint and will be summarized for each tumor type using the response evaluable population. TTR will be summarized by descriptive statistics, and DOR will be summarized by Kaplan-Meier method for patients with complete response (CR) or partial response (PR) as BOR. OS and PFS will be summarized for each tumor type by the Kaplan-Meier method using all treated patients. Pharmacokinetic parameters will be summarized with descriptive statistics by tumor cohort. [redacted]

Figure 1: Study Schematic



1.1 Schedule of Events

Table 1: Schedule of Events for Dose Optimization Cohorts

Assessment Period	**Screening**	**Cycle 1 (3 + 3) OR at the Start of Each Cycle a Patient is Administered a Step-up Dose**					**Cycle 2 and Beyond**	**Post-treatment**	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 3**	**Day 5 (± 1 day)**	**Day 8 (± 1 day)**	**Day 15 to 21**	**Day 1 (± 3 days)**	**EOT[b] 30 (± 10) days**	**Long-term Follow-up 90 (± 10) days[c]**
General Assessments									
Obtain informed consent	X								
Physical examination[d]	X	X	X		X		X	X	
Vital signs[e]	X	X	X		X		X	X	
ECOG performance status	X						X		
ECG[f]	X								
ECHO/MUGA[g]	X								
Oral hydration follow-up[h]			X	X			X		
Adverse events review	<----------								---------->
Concomitant medications/procedures review	<----------								---------->
Quarterly follow-up[c]									X
Laboratory Tests and [redacted] Samples									
Pregnancy test[i]	X	X					X	X	
Hematology[j]	X	X	X	X	X		X	X	
Serum chemistry[k]	X	X		X	X		X	X	

Table 1: Schedule of Events for the Dose Optimization Cohorts (Contd)

Assessment Period	Screening	Cycle 1 (3 + 3) OR at the Start of Each Cycle a Patient is Administered a Step-up Dose					Cycle 2 and Beyond	Post-treatment	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 3**	**Day 5 (± 1 day)**	**Day 8 (± 1 day)**	**Day 15 to 21**	**Day 1 (± 3 days)**	**EOT[b] 30 (± 10) days**	**Long-term Follow-up 90 (± 10) days[c]**
Coagulation[k]	X	X		X	X		X	X	
Additional tests[l]	X	X			X		X	X	
Urinalysis (dipstick)[m]	X	X					X	X	
Serology[k]	X								
Tumor biopsy[n]	X					X			
Immunogenicity serum sample[o]		X					X	X	X
[redacted]		[redacted]			[redacted]				
[redacted]		[redacted]							
NKTR-214 PK blood sample[r]		X	X	X	X[r]		X		
Imaging									
Tumor assessment[s]	X						Every 9 weeks (± 7d)	X	X
Drug Administration									
Administer IV fluids[t]		X					X		
Prophylactic acetaminophen/NSAIDS[u]		X	X	X			X		
Drug administration[u]		X					X		

Footnotes:

a. **Study Days:** Cycles are 21 days. Each cycle after Cycle 1 Day 1 must occur within 21 days (± 3 days) from the previous dose. Cycle intervals less than 21 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. If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation. Study assessments, including imaging, may also be delayed or performed prior to the assessment window with permission from the medical monitor. All procedures and examinations should be performed before the administration of study drug(s), except as indicated.

b. **EOT Visit**: The EOT visit should occur 30 (± 10) days after last dose of all study medications or before a new antineoplastic regimen (including commercially-sourced single-agent pembrolizumab) starts. EOT NKTR-214 immunogenicity sample must be drawn 30 (± 10) days after the last dose of NKTR-214. See Section 5.4.

c. **Long-Term Follow up**: Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. Timing for long-term follow-up will be as follows: Upon discontinuation of all study treatment, the long-term follow-up visits should occur every 90 (± 10) days after the last dose of all study treatment and then every 90 (± 10) days for survival status. Per clinical judgment, the patient may come in earlier. If a patient did not experience PD by RECIST 1.1 when study drug treatment was discontinued, tumor assessments should continue every 90 (± 10) days until PD, consent withdrawal, start of new antineoplastic regimen, death, or study termination by Sponsor. Immunogenicity sample must be drawn 90 days (± 10) days after the last administered dose of NKTR-214. See Section 5.5.

d. **Physical Examination**: Full physical examinations should be conducted at screening, and Days 1, 3 and 8 of Cycle 1. At Cycle 2 and beyond, full physical examinations are conducted on Day 1 of each cycle, and EOT. 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. Weight is to be reported at each dosing visit (for weight changes of ± 10% from baseline, recalculation of dose is not required), height at screening visit only. See Section 7.15.

e. **Vital Signs**: Some clinic visits will have more frequent vital sign measurements. Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure (supine position), oxygen saturation (on dosing days only), and temperature (oral preferred). On dosing days vital signs are to be taken and recorded prior to NKTR-214 dosing and monitored and recorded following completion of pembrolizumab administration. For the frequency (Cycle 1 Day 1, 3, 8 and Cycle ≥ 2 Day 1), see Sections 5.3.4.1 and 7.16.

f. **ECG:** A screening 12-lead ECG must be done during the 28-day screening window prior to Cycle 1 Day 1. Patients must be resting quietly in the supine position for at least 5 minutes before the ECG collection. See Section 7.17.

g. **ECHO/MUGA**: A standard echocardiogram (ECHO) or multigated acquisition (MUGA) will be performed for all patients within 90 days prior to dosing on Cycle 1 Day 1 to assess for cardiac function and left ventricular ejection fraction (LVEF). 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 ECHO cannot be performed. See Section 7.18.

h. **Oral Hydration Follow-up**: Patients will be asked about in-home hydration guideline compliance on Day 5 (see Section 5.3.4.2). In addition, between 2 and 4 days (inclusive) following treatment with NKTR-214, 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.

i. **Pregnancy Tests**: Local serum pregnancy test required at screening (anytime during 28-day screening window; ICF signature not required), and urine pregnancy tests are required before dosing on Day 1 of each cycle and EOT for women of childbearing potential (WCBP). See Section 7.19.

j. **Hematology**: Local 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.

k. **Serum Chemistry, Coagulation, and Serology**: Serology may be performed at any time during the screening period (ICF signature not required). The local sampling for serum chemistry and coagulation tests should be drawn within 72 hours prior to dosing. See Appendix 1.

l. **Additional Tests**: Additional local tests are performed at Screening (anytime during 28-day screening window; ICF signature not required), on Day 1 and Day 8 of Cycle 1 Day 1 starting with Cycle 2 and beyond, and at EOT. The sampling for additional tests can be drawn within 72 hours prior to dosing. See Appendix 1.

m. **Urinalysis**: Microscopy is required only to follow-up clinically significant urine dipstick findings (Appendix 1).

n. **Tumor Biopsy**: All patients must provide tumor tissue from resection or biopsy obtained within 12 months from screening as either formalin-fixed paraffin-embedded (FFPE) block or unstained slides (a minimum of 10 slides freshly-cut within 1 week of submission) (Table 13). Tissue obtained from fine needle aspiration, cytology specimen and bone lesion are NOT acceptable. Unused portions of the block will be returned to the site. If archival tissue is not available, or if patient received systemic anticancer therapy between dates of tissue collection and screening, a fresh biopsy is required. If screening biopsies (fresh or archival) are not obtained, on-treatment biopsies should not be collected. The biopsy sampling schedule is provided in Section 5.10.2.

o. **Immunogenicity Serum Samples**: Immunogenicity samples for NKTR-214 will be drawn at predose on Day 1 of Cycle 1 and Cycle 2, and predose on Day 1 of every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc.), at the NKTR-214 EOT visit, and at 90 (± 10) days after the last administered dose of NKTR-214. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing. If dosing occurs on a different day, the immunogenicity sampling should be adjusted accordingly. See Section 5.9.

p. [redacted]

q. [redacted]

r. **NKTR-214 PK sample**: For the dose optimization 3 + 3 cohort, for Cycle 1 and only the first cycle of subsequent cycle(s) in which the patient is administered a step-up dose, blood will be collected on Days 1 (predose), 3, 5 and 8 and at the following times after the start of the NKTR-214 infusion: 3 hr ± 30 min (Day 1), 48 hr ± 3 hr (Day 3), 96 hr ± 24 hr (Day 5), and 168 hr ± 24 hr (Day 8). With the exception of the first cycles in which the patient is administered a step-up dose, blood will be collected predose on Day 1 on Cycle 2 and every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc.). For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing. If a possible study drug(s)-related SAE occurs on study, PK blood samples should be drawn as close to the event as possible to help characterize any possible relationships between drug exposure and the SAE. See Section 5.8 for additional details.

s. **Tumor Assessment**: Tumor assessment at screening then every 9 weeks (± 7 days) from Cycle 1 Day 1, EOT (unless scan done within 4 weeks) and at the 90-day long-term follow-up visits, (see Section 5.7). If a patient has an unconfirmed PR or CR, an early scan is recommended 4 weeks or later, and the next scheduled 9-week scan may be skipped if less than 4 weeks from the early scan. All subsequent tumor assessments must remain on the original 9-week assessment schedule. Patients with unconfirmed subsequent tumor assessments must remain on the original 9-week assessment schedule unless an early scan is clinically indicated. A brain MRI at screening is required for all patients with metastatic NSCLC, and for patients with other tumor types who have known brain metastasis only. Subsequent brain MRIs for all cohorts can be done at 9-week intervals as clinically indicated. Assessments will become less frequent during the long-term follow-up period. Changes in tumor assessments (either PR or CR) must be confirmed by repeat assessments that should be performed ≥ 4 weeks after criteria for response are first met. See Section 8.2.2.3.

t. **Administer IV Fluids**: Patients should receive administration of 1 liter of normal saline IV with study treatment infusion on Day 1 of each cycle. In addition, consider administering 1 liter of normal saline IV when the patients return for clinic visits (ex. if the patient returns for PK draws on Days 3 and 5 of Cycle 1), anytime based on the patients need, or as clinically indicated. See Section 5.3.4.2.

u. **Prophylactic Acetaminophen/NSAIDS**: Patients will be premedicated with acetaminophen (eg, 650 mg every 6 hours) or NSAIDs (eg, ibuprofen 400 mg every 6 hours) on Day 1 of each cycle. In addition, acetaminophen or NSAIDs will be administered on Day 2 to 5 of each cycle every 6 hours. See Section 5.3.4.3.

v. **Drug Administration**: When administered on the same day, NKTR-214 will be administered first (30 ± 5 minutes) followed by pembrolizumab (30 ± 5 minutes). See Section 5.3.1. After NKTR-214 administration, flush the intravenous line with an appropriate amount of the same diluent used for dose preparation to ensure that the total dose is completely administered over the appropriate time. No delay is necessary between drug administrations after checking for stable vitals.

Abbreviations: CVA = cerebrovascular event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiography; EOT = End of Treatment; IV = intravenous; MUGA = multigated acquisition; NSAIDS = nonsteroidal anti-inflammatory drugs; PK = pharmacokinetic.

Table 2: Schedule of Events for Dose Expansion Cohorts 2 and 3

Assessment Period	**Screening**	**Cycle 1**				**Cycle 2 and Beyond**	**Post-treatment**	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 3**	**Day 5 (±1 day)**	**Day 8 (± 1 day)**	**Day 1 (±3 days)**	**EOT[b] 30 (± 10) days**	**Long-term Follow up 90 (± 10) days[c]**
General Assessments								
Obtain informed consent	X							
Physical examination[d]	X	X	X		X	X	X	
Vital signs[e]	X	X	X		X	X	X	
ECOG performance status	X					X		
ECG[f]	X							
ECHO/MUGA[g]	X							
Oral hydration follow-up[h]			X	X		X		
Adverse events review	<----------							---------->
Concomitant medications/procedures review	<----------							---------->
Quarterly follow-up[c]								X
Laboratory Tests and [redacted] Samples								
Pregnancy test[i]	X	X				X	X	
Hematology[j]	X	X	X	X	X	X	X	
Serum chemistry[k]	X	X		X	X	X	X	
Coagulation[k]	X	X		X	X	X	X	
Additional tests[l]	X	X			X	X	X	

Table 2: Schedule of Events for Dose Expansion Cohorts 2 and 3 (Contd)

Assessment Period	Screening	Cycle 1				Cycle 2 and Beyond	Post-treatment	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 3**	**Day 5 (±1 day)**	**Day 8 (±1 day)**	**Day 1 (±3 days)**	**EOT[b] 30 (± 10 days)**	**Long-term Follow up 90 (± 10) days[c]**
Urinalysis (dipstick)[m]	X	X				X	X	
Serology[k]	X							
Tumor biopsy[n]	X							
Immunogenicity serum sample[o]		X				X	X	X
[redacted]		[redacted]			[redacted]			
[redacted]		[redacted]						
NKTR-214 PK blood sample[r]		X	X	X	X[r]	X		
Imaging								
Tumor assessment[s]	X					Every 9 weeks (± 7d)	X	X
Drug Administration								
Administer IV fluids[t]		X				X		
Prophylactic acetaminophen/NSAIDS[u]		X	X	X		X		
Drug administration[v]		X				X		
Serum cortisol level (morning) For Australia only[w]		X				X		

Footnotes:

a. **Study Days**: Cycles are 21 days. Each cycle after Cycle 1 Day 1 must occur within 21 days (± 3 days) from the previous dose. Cycle intervals less than 21 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. If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation. Study assessments, including imaging, may also be delayed or performed prior to the assessment window with permission from the medical monitor. All procedures and examinations should be performed before the administration of study drug(s), except as indicated.

b. **EOT Visit**: The EOT visit should occur 30 (± 10) days after the last dose of all study medications or before a new antineoplastic regimen (including commercially-sourced single-agent pembrolizumab) starts. EOT NKTR-214 immunogenicity sample must be drawn 30 (± 10 days) after the last dose of NKTR-214. See Section 5.4.

c. **Long-Term Follow up**: Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. Timing for long-term follow-up will be as follows: Upon discontinuation of all study treatment, the long-term follow-up visits should occur every 90 (± 10) days for survival status. Per clinical judgment, the patient may come in earlier. If a patient did not experience PD by RECIST 1.1 when study drug treatment was discontinued, tumor assessments should continue every 90 (± 10) days until PD, consent withdrawal, start of new antineoplastic regimen, death, or study termination by Sponsor. See Section 5.5. Immunogenicity sample must be drawn 90 days (± 10 days) after the last administered dose of NKTR-214.

d. **Physical Examination**: Full physical examinations should be conducted at screening, and Days 1, 3 and 8 of Cycle 1. In Cycle 2 and beyond, full physical examinations are conducted on Day 1 of each cycle, and EOT. 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. Weight is to be reported at each dosing visit, height at screening visit only. See Section 7.15.

e. **Vital Signs**: Some clinic visits will have more frequent vital sign measurements. Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure (supine position), oxygen saturation (on dosing days only), and temperature (oral preferred). On dosing days vital signs are to be taken and recorded prior to NKTR-214 dosing and monitored and recorded following completion of pembrolizumab administration. For the frequency (Cycle 1 Day 1, 3, 8 and Cycle ≥ 2 Day 1), see Sections 5.3.4.1 and 7.16.

f. **ECG**: A screening 12 -lead ECG must be done during the 28-day screening window prior to Cycle 1 Day 1. Patients must be resting quietly in the supine position for at least 5 minutes before the ECG collection. On-treatment ECG monitoring may be initiated if clinically indicated. See Section 7.17.

g. **ECHO/MUGA**: A standard echocardiogram (ECHO) or multigated acquisition (MUGA) will be performed for all patients within 90 days prior to dosing on Cycle 1 Day 1 to assess for cardiac function and left ventricular ejection fraction (LVEF). 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 ECHO cannot be performed. See Section 7.18.

h. **Oral Hydration Follow-up**: Patients will be asked about in-home hydration guideline compliance on Day 5 (see Section 5.3.4.2). In addition, between 2 and 4 days (inclusive) following treatment with NKTR-214, 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.

i. **Pregnancy Tests**: A local serum pregnancy test is required at screening (anytime during 28-day screening window; ICF signature not required), and urine pregnancy tests are required before dosing on Day 1 of each cycle and EOT for women of childbearing potential (WCBP). See Section 7.19.

j. **Hematology:** Local 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.

k. **Serum Chemistry, Coagulation and Serology**: Serology may be performed at any time during the screening period (ICF signature not required). The local sampling of serum chemistry and coagulation laboratory tests should be drawn within 72 hours prior to dosing. See Appendix 1.

l. **Additional Tests**: Additional local tests are performed at Screening (anytime during 28-day screening window; ICF signature not required), on Day 1 and Day 8 of Cycle 1 Day 1 starting with Cycle 2 and beyond, and at EOT. The sampling for additional tests can be drawn within 72 hours prior to dosing. See Appendix 1.

m. **Urinalysis**: Microscopy is required only to follow up clinically significant urine dipstick findings. See Appendix 1.

n. **Tumor Biopsy**: All patients must provide tumor tissue from resection or biopsy obtained within 12 months from screening as either formalin-fixed paraffin-embedded (FFPE) block or unstained slides (a minimum of 10 slides freshly-cut within 1 week of submission) prior to enrollment (Table 13). Tissue obtained from fine needle aspiration, cytology specimen and bone lesion are NOT acceptable. Unused portions of the block will be returned to the site. If archival tissue is not available, or if patient received systemic anticancer therapy between dates of tissue collection and screening, a fresh biopsy is required. The biopsy sampling schedule is provided in Section 5.10.2.

o. **Immunogenicity Serum Samples**: Immunogenicity samples for NKTR-214 will be drawn at predose on Day 1 of Cycle 1, and Cycle 2, and predose on Day 1 of every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc.), at the NKTR-214 EOT visit, and at 90 (± 10) days after the last administered dose of NKTR-214. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing. If dosing occurs on a different day, the immunogenicity sampling should be adjusted accordingly. See Section 5.9.

p. [redacted]

q. [redacted]

r. **NKTR-214 PK sample**: For Cycle 1 only, blood will be collected on Days 1 (predose), 3, 5, and 8 and at the following times after the start of the NKTR-214 infusion 3 hr ± 30 min (Day 1), 48 hr ± 3 hr (Day 3), 96 hr ± 24 hr (Day 5) and 168 hr ± 24 hr (Day 8). For Cycle 2 and every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc) blood will be collected predose on Day 1. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing. If a possible study drug(s)-related SAE occurs on study, PK blood samples should be drawn as close to the event as possible to help characterize any possible relationships between drug exposure and the SAE. See Section 5.8 for additional details.

s. **Tumor Assessment**: Tumor assessment at screening then every 9 weeks (± 7 days) from Cycle 1 Day 1, EOT (unless scan done within 4 weeks) and at the 90-day long-term follow-up visits, (see Section 5.7). If a patient has an unconfirmed PR or CR, an early scan is recommended 4 weeks or later, and the next scheduled 9-week scan may be skipped if less than 4 weeks from the early scan. All subsequent tumor assessments must remain on the original 9-week assessment schedule. Patients with unconfirmed subsequent tumor assessments must remain on the original 9-week assessment schedule unless an early scan is clinically indicated. A brain MRI at screening is required for all patients with metastatic NSCLC, and for patients with other tumor types who have known brain metastasis only. Subsequent brain MRIs for all cohorts can be done at 9-week intervals as clinically indicated. Assessments will become less frequent during the long-term follow-up period. Changes in tumor assessments (either PR or CR) must be confirmed by repeat assessments that should be performed ≥ 4 weeks after criteria for response are first met. See Section 8.2.2.3.

t. **Administer IV Fluids**: Patients should receive administration of 1 liter of normal saline IV with study treatment infusion on Day 1 of each cycle. In addition, consider administering 1 liter of normal saline IV when the patients return for clinic visits (ex. if the patient returns for PK draws on Days 3 and 5 of Cycle 1), anytime based on the patients need, or as clinically indicated. See Section 5.3.4.2.

u. **Prophylactic Acetaminophen/NSAIDS**: Patients will be premedicated with acetaminophen (eg, 650 mg every 6 hours) or NSAIDs (eg, ibuprofen 400 mg every 6 hours) on Day 1 of each cycle. In addition, administer acetaminophen or NSAIDs on Day 2 to 5 of each cycle.

v. **Drug Administration**: When administered on the same day, NKTR-214 will be administered first (30 ± 5 minutes) followed by pembrolizumab (30 ± 5 minutes). See Section 5.3.1. After NKTR-214 administration, flush the intravenous line with an appropriate amount of the same diluent used for dose preparation to ensure that the total dose is completely administered over the appropriate time. No delay is necessary between drug administrations after checking for stable vitals.

w. **For Australia Only: Serum Cortisol Level**: The Belberry HREC requires that all study Investigators in Australia follow the current NCCN guidelines relating to the management of immune checkpoint inhibitor-related toxicities, specifically related to serum cortisol monitoring. Please refer to the current version of the above-mentioned guidelines (Thompson 2020) and ensure that compliance with the guidelines is documented in the patient source documentation. Serum cortisol monitoring should be performed in Cycles 1, 2, 3, and 4 only.

Abbreviations: CVA = cerebrovascular event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiography; EOT = End of Treatment; IV = intravenous; MUGA = multigated acquisition; NSAIDS = nonsteroidal anti-inflammatory drugs; PK = pharmacokinetic

Table 3: Schedule of Events for Dose Expansion Cohort 4

Assessment Period	**Screening**	**Cycle 1**				**Cycle 2 and Beyond**	**Post-treatment**	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 3**	**Day 5 (± 1 day)**	**Day 8 (± 1 day)**	**Day 1 (± 3 days)**	**EOT[b] 30 (± 10) days**	**Long-term Follow up 90 (± 10) days[c]**
General Assessments								
Obtain informed consent	X							
Physical examination[d]	X	X	X		X	X	X	
Vital signs[e]	X	X	X		X	X	X	
ECOG performance status	X					X		
ECG[f]	X							
ECHO/MUGA[g]	X							
Oral hydration follow-up[h]			X	X		X		
Adverse events review	<----------							---------->
Concomitant medications/procedures review	<----------							---------->
Quarterly follow-up[c]								X
Laboratory Tests and [redacted] Samples								
Pregnancy test[i]	X	X				X	X	
Hematology[j]	X	X	X	X	X	X	X	
Serum chemistry[k]	X	X		X	X	X	X	
Coagulation[k]	X	X		X	X	X	X	
Additional tests[l]	X	X			X	X	X	

Table 3: Schedule of Events for Dose Expansion Cohort 4 (Contd)

Assessment Period	Screening	Cycle 1				Cycle 2 and Beyond	Post-treatment	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 3**	**Day 5 (± 1 day)**	**Day 8 (± 1 day)**	**Day 1 (± 3 days)**	**EOT[b] 30 (± 10 days)**	**Long-term Follow up 90 (± 10) days[c]**
Urinalysis (dipstick)[m]	X	X				X	X	
Serology[k]	X							
Tumor biopsy[n]	X							
Immunogenicity serum sample[o]		X				X	X	X
[redacted]		[redacted]			[redacted]			
[redacted]		[redacted]						
NKTR-214 PK blood sample[r]		X	X	X	X[r]	X		
Imaging								
Tumor assessment[s]	X					Every 9 weeks (± 7d)	X	X
Drug Administration								
Administer IV fluids[t]		X				X		
Prophylactic acetaminophen/NSAIDS[u]		X	X	X		X		
Drug administration[v]		X				X		
Serum AM cortisol level For Australia only[w]		X				X		

Footnotes:

a. **Study Days**: Cycles are 21 days. Each cycle after Cycle 1 Day 1 must occur within 21 days (± 3 days) from the previous dose. Cycle intervals less than 21 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. If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation. Study assessments, including imaging, may also be delayed or performed prior to the assessment window with permission from the medical monitor. All procedures and examinations should be performed before the administration of study drug(s), except as indicated.

b. **EOT Visit**: The EOT visit should occur 30 (± 10) days after the last dose of all study medications or before a new antineoplastic regimen (including commercially-sourced single-agent pembrolizumab) starts. EOT NKTR-214 immunogenicity sample must be drawn 30 (± 10 days) after the last dose of NKTR-214. See Section 5.4.

c. **Long-Term Follow up**: Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. Timing for long-term follow-up will be as follows: Upon discontinuation of all study treatment, the long-term follow-up visits should occur every 90 (± 10) days for survival status. Per clinical judgment, the patient may come in earlier. If a patient did not experience PD by RECIST 1.1 when study drug treatment was discontinued, tumor assessments should continue every 90 (± 10) days until PD, consent withdrawal, start of new antineoplastic regimen, death, or study termination by Sponsor. See Section 5.5. Immunogenicity sample must be drawn 90 days (± 10 days) after the last administered dose of NKTR-214.

d. **Physical Examination**: Full physical examinations should be conducted at screening, and Days 1, 3 and 8 of Cycle 1. In Cycle 2 and beyond, full physical examinations are conducted on Day 1 of each cycle, and EOT. 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. Weight is to be reported at each dosing visit, height at screening visit only. See Section 7.15.

e. **Vital Signs**: Some clinic visits will have more frequent vital sign measurements. Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure (supine position), oxygen saturation (on dosing days only), and temperature (oral preferred). On dosing days vital signs are to be taken and recorded prior to NKTR-214 dosing and monitored and recorded following completion of pembrolizumab administration. For the frequency (Cycle 1 Day 1, 3, 8 and Cycle ≥ 2 Day 1), see Sections 5.3.4.1 and 7.16.

f. **ECG**: A screening 12 -lead ECG must be done during the 28-day screening window prior to Cycle 1 Day 1. Patients must be resting quietly in the supine position for at least 5 minutes before the ECG collection. On-treatment ECG monitoring may be initiated if clinically indicated. See Section 7.17.

g. **ECHO/MUGA**: A standard echocardiogram (ECHO) or multigated acquisition (MUGA) will be performed for all patients within 90 days prior to dosing on Cycle 1 Day 1 to assess for cardiac function and left ventricular ejection fraction (LVEF). 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 ECHO cannot be performed. See Section 7.18.

h. **Oral Hydration Follow-up**: Patients will be asked about in-home hydration guideline compliance on Day 5 (see Section 5.3.4.2). In addition, between 2 and 4 days (inclusive) following treatment with NKTR-214, 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.

i. **Pregnancy Tests**: A local serum pregnancy test is required at screening (anytime during 28-day screening window; ICF signature not required), and urine pregnancy tests are required before dosing on Day 1 of each cycle and EOT for women of childbearing potential (WCBP). See Section 7.19.

j. **Hematology:** Local 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.

k. **Serum Chemistry, Coagulation and Serology**: Serology may be performed at any time during the screening period (ICF signature not required). The local sampling for serum chemistry and coagulation tests should be drawn within 72 hours prior to dosing. See Appendix 1.

l. **Additional Tests**: Additional local tests are performed at Screening, on Day 1 and Day 8 of Cycle 1 Day 1 starting with Cycle 2 and beyond, and at EOT. The sampling for additional tests can be drawn within 72 hours prior to dosing. See Appendix 1.

m. **Urinalysis**: Microscopy is required only to follow up clinically significant urine dipstick findings. See Appendix 1.

n. **Tumor Biopsy**: All patients must provide tumor tissue from resection or biopsy obtained within 12 months from screening as either formalin-fixed paraffin-embedded (FFPE) block or unstained slides (a minimum of 10 slides freshly-cut within 1 week of submission) prior to enrollment (Table 13). Tissue obtained from fine needle aspiration, cytology specimen and bone lesion are NOT acceptable. Unused portions of the block will be returned to the site. If archival tissue is not available, or if patient received systemic anticancer therapy between dates of tissue collection and screening, a fresh biopsy is required. The biopsy sampling schedule is provided in Section 5.10.2.

o. **Immunogenicity Serum Samples**: Immunogenicity samples for NKTR-214 will be drawn at predose on Day 1 of Cycle 1, and Cycle 2, and predose on Day 1 of every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc.), at the NKTR-214 EOT visit, and at 90 (± 10) days after the last administered dose of NKTR-214. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing. If dosing occurs on a different day, the immunogenicity sampling should be adjusted accordingly. See Section 5.9.

p [redacted].

q [redacted]

r. **NKTR-214 PK sample**: For Cycle 1 only, blood will be collected on Days 1 (predose), 3, 5, and 8 and at the following times after the start of the NKTR-214 infusion 3 hr ± 30 min (Day 1), 48 hr ± 3 hr (Day 3), 96 hr ± 24 hr (Day 5) and 168 hr ± 24 hr (Day 8). For Cycle 2 and every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc) blood will be collected predose on Day 1. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing. If a possible study drug(s)-related SAE occurs on study, PK blood samples should be drawn as close to the event as possible to help characterize any possible relationships between drug exposure and the SAE. See Section 5.8 for additional details.

s. **Tumor Assessment**: Tumor assessment at screening then every 9 weeks (± 7 days) from Cycle 1 Day 1, EOT (unless scan done within 4 weeks) and at the 90-day long-term follow-up visits, (see Section 5.7). If a patient has an unconfirmed PR or CR, an early scan is recommended 4 weeks or later, and the next scheduled 9-week scan may be skipped if less than 4 weeks from the early scan. All subsequent tumor assessments must remain on the original 9 -week assessment schedule. Patients with unconfirmed subsequent tumor assessments must remain on the original 9-week assessment schedule unless an early scan is clinically indicated. A brain MRI at screening is required for all patients with metastatic NSCLC, and for patients with other tumor types who have known brain metastasis only. Subsequent brain MRIs for all cohorts can be done at 9-week intervals as clinically indicated. Assessments will become less frequent during the long-term follow-up period. Changes in tumor assessments (either PR or CR) must be confirmed by repeat assessments that should be performed ≥ 4 weeks after criteria for response are first met. See Section 8.2.2.3.

t. **Administer IV Fluids**: Patients should receive administration of 1 liter of normal saline IV with study treatment infusion on Day 1 of each cycle. In addition, consider administering 1 liter of normal saline IV when the patients return for clinic visits (ex. if the patient returns for PK draws on Days 3 and 5 of Cycle 1), anytime based on the patients need, or as clinically indicated. See Section 5.3.4.2.

u. **Prophylactic Acetaminophen/NSAIDS**: Patients will be premedicated with acetaminophen (eg, 650 mg every 6 hours) on Day 1 of each cycle. In addition, administer acetaminophen on Day 2 to 5 of each cycle.

v. **Drug Administration**: When administered on the same day, NKTR-214 will be administered first (30 ± 5 minutes) followed by pembrolizumab (30 ± 5 minutes). See Section 5.3.1. After NKTR-214 administration, flush the intravenous line with an appropriate amount of the same diluent used for dose preparation to ensure that the total dose is completely administered over the appropriate time. No delay is necessary between drug administrations after checking for stable vitals. Chemotherapy drugs will be administered after Pembrolizumab following local practice and labels.

w. **For Australia Only: Serum Cortisol Level**: The Belberry HREC requires that all study Investigators in Australia follow the current NCCN guidelines relating to the management of immune checkpoint inhibitor-related toxicities, specifically related to serum cortisol monitoring. Please refer to the current version of the above-mentioned guidelines (Thompson 2020) and ensure that compliance with the guidelines is documented in the patient source documentation. Serum cortisol monitoring should be performed in Cycles 1, 2, 3, and 4 only.

Abbreviations: CVA = cerebrovascular event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiography; EOT = End of Treatment; IV = intravenous; MUGA = multigated acquisition; NSAIDS = nonsteroidal anti-inflammatory drugs; PK = pharmacokinetic

Table 4: Schedule of Events for Dose Expansion Cohort 5

Assessment Period	**Screening**	**Cycle 1**				**Cycle 2 and Beyond**	**Post-treatment**	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 3**	**Day 5 (± 1 day)**	**Day 8 (± 1 day)**	**Day 1 (± 3 days)**	**EOT[b] 30 (± 10) days**	**Long-term Follow up 90 (± 10) days[c]**
General Assessments								
Obtain informed consent	X							
Physical examination[d]	X	X	X		X	X	X	
Vital signs[e]	X	X	X		X	X	X	
ECOG performance status	X					X		
ECG[f]	X							
ECHO/MUGA[g]	X							
Oral hydration follow-up[h]			X	X		X		
Adverse events review	<----------							---------->
Concomitant medications/procedures review	<----------							---------->
Quarterly follow-up[c]								X
Laboratory Tests and [redacted] Samples								
Pregnancy test[i]	X	X				X	X	
Hematology[j]	X	X	X	X	X	X	X	
Serum chemistry[k]	X	X		X	X	X	X	
Coagulation[k]	X	X		X	X	X	X	
Additional tests[l]	X	X			X	X	X	

Table 4: Schedule of Events for Dose Expansion Cohort 5 (Contd)

Assessment Period	Screening	Cycle 1				Cycle 2 and Beyond	Post-treatment	
Study Days[a]	**Day -28 to -1**	**Day 1**	**Day 3**	**Day 5 (± 1 day)**	**Day 8 (± 1 day)**	**Day 1 (± 3 days)**	**EOT[b] 30 (± 10 days)**	**Long-term Follow up 90 (± 10) days[c]**
Urinalysis (dipstick)[m]	X	X				X	X	
Serology[k]	X							
Tumor biopsy[n]	X							
Immunogenicity serum sample[o]		X				X	X	X
[redacted]		[redacted]			[redacted]			
[redacted]		[redacted]						
NKTR-214 PK blood sample[r]		X	X	X	X[r]	X		
Imaging								
Tumor assessment[s]	X					Every 9 weeks (± 7d)	X	X
Drug Administration								
Administer IV fluids[t]		X				X		
Prophylactic acetaminophen/NSAIDS[u]		X	X	X		X		
Drug administration[v]		X				X		
Serum AM cortisol level For Australia only[w]		X				X		

Footnotes:

a. **Study Days**: Cycles are 21 days. Each cycle after Cycle 1 Day 1 must occur within 21 days (± 3 days) from the previous dose. Cycle intervals less than 21 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. If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation. Study assessments, including imaging, may also be delayed or performed prior to the assessment window with permission from the medical monitor. All procedures and examinations should be performed before the administration of study drug(s), except as indicated.

b. **EOT Visit**: The EOT visit should occur 30 (± 10) days after the last dose of all study medications or before a new antineoplastic regimen (including commercially-sourced single-agent pembrolizumab) starts. EOT NKTR-214 immunogenicity sample must be drawn 30 (± 10 days) after the last dose of NKTR-214. See Section 5.4.

c. **Long-Term Follow up**: Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. Timing for long-term follow-up will be as follows: Upon discontinuation of all study treatment, the long-term follow-up visits should occur every 90 (± 10) days for survival status. Per clinical judgment, the patient may come in earlier. If a patient did not experience PD by RECIST 1.1 when study drug treatment was discontinued, tumor assessments should continue every 90 (± 10) days until PD, consent withdrawal, start of new antineoplastic regimen, death, or study termination by Sponsor. See Section 5.5. Immunogenicity sample must be drawn 90 days (± 10 days) after the last administered dose of NKTR-214.

d. **Physical Examination**: Full physical examinations should be conducted at screening, and Days 1, 3 and 8 of Cycle 1. In Cycle 2 and beyond, full physical examinations are conducted on Day 1 of each cycle, and EOT. 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. Weight is to be reported at each dosing visit, height at screening visit only. See Section 7.15.

e. **Vital Signs**: Some clinic visits will have more frequent vital sign measurements. Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure (supine position), oxygen saturation (on dosing days only), and temperature (oral preferred). On dosing days vital signs are to be taken and recorded prior to NKTR-214 dosing and monitored and recorded following completion of pembrolizumab administration. For the frequency (Cycle 1 Day 1, 3, 8 and Cycle ≥ 2 Day 1), see Sections 5.3.4.1 and 7.16.

f. **ECG**: A screening 12 -lead ECG must be done during the 28-day screening window prior to Cycle 1 Day 1. Patients must be resting quietly in the supine position for at least 5 minutes before the ECG collection. On-treatment ECG monitoring may be initiated if clinically indicated. See Section 7.17.

g. **ECHO/MUGA**: A standard echocardiogram (ECHO) or multigated acquisition (MUGA) will be performed for all patients within 90 days prior to dosing on Cycle 1 Day 1 to assess for cardiac function and left ventricular ejection fraction (LVEF). 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 ECHO cannot be performed. See Section 7.18.

h. **Oral Hydration Follow-up**: Patients will be asked about in-home hydration guideline compliance on Day 5 (see Section 5.3.4.2). In addition, between 2 and 4 days (inclusive) following treatment with NKTR-214, 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.

i. **Pregnancy Tests**: A local serum pregnancy test required at screening (anytime during 28-day screening window; ICF signature not required), and urine pregnancy tests are required before dosing on Day 1 of each cycle and EOT for women of childbearing potential (WCBP). See Section 7.19.

j. **Hematology:** Local 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.

k. **Serum Chemistry, Coagulation and Serology**: Serology may be performed at any time during the screening period (ICF signature not required). The local sampling for serum chemistry and coagulation tests should be drawn within 72 hours prior to dosing. See Appendix 1.

l. **Additional Tests**: Additional local tests are performed at Screening (anytime during 28-day screening window; ICF signature not required), on Day 1 and Day 8 of Cycle 1 Day 1 starting with Cycle 2 and beyond, and at EOT. The sampling for additional tests can be drawn within 72 hours prior to dosing. See Appendix 1.

m. **Urinalysis**: Microscopy is required only to follow up clinically significant urine dipstick findings. See Appendix 1.

n. **Tumor Biopsy**: All patients must provide tumor tissue from resection or biopsy obtained within 12 months from screening as either formalin-fixed paraffin-embedded (FFPE) block or unstained slides (a minimum of 10 slides freshly-cut within 1 week of submission) prior to enrollment (Table 13). Tissue obtained from fine needle aspiration, cytology specimen and bone lesion are NOT acceptable. Unused portions of the block will be returned to the site. If archival tissue is not available, or if patient received systemic anticancer therapy between dates of tissue collection and screening, a fresh biopsy is required. The biopsy sampling schedule is provided in Section 5.10.2.

o. **Immunogenicity Serum Samples**: Immunogenicity samples for NKTR-214 will be drawn at predose on Day 1 of Cycle 1, and Cycle 2, and predose on Day 1 of every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc.), at the NKTR-214 EOT visit, and at 90 (± 10) days after the last administered dose of NKTR-214. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing. If dosing occurs on a different day, the immunogenicity sampling should be adjusted accordingly. See Section 5.9.

p. [redacted]

q. [redacted]

r. **NKTR-214 PK sample**: For Cycle 1 only, blood will be collected on Days 1 (predose), 3, 5, and 8 and at the following times after the start of the NKTR-214 infusion 3 hr ± 30 min (Day 1), 48 hr ± 3 hr (Day 3), 96 hr ± 24 hr (Day 5) and 168 hr ± 24 hr (Day 8). For Cycle 2 and every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc) blood will be collected predose on Day 1. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing. If a possible study drug(s)-related SAE occurs on study, PK blood samples should be drawn as close to the event as possible to help characterize any possible relationships between drug exposure and the SAE. See Section 5.8 for additional details.

s. **Tumor Assessment**: Tumor assessment at screening then every 9 weeks (± 7 days) from Cycle 1 Day 1, EOT (unless scan done within 4 weeks) and at the 90-day long-term follow-up visits, (see Section 5.7). If a patient has an unconfirmed PR or CR, an early scan is recommended 4 weeks or later, and the next scheduled 9-week scan may be skipped if less than 4 weeks from the early scan. All subsequent tumor assessments must remain on the original 9-week assessment schedule. Patients with unconfirmed subsequent tumor assessments must remain on the original 9-week assessment schedule unless an early scan is clinically indicated. A brain MRI at screening is required for all patients with metastatic NSCLC, and for patients with other tumor types who have known brain metastasis only. Subsequent brain MRIs for all cohorts can be done at 9-week intervals as clinically indicated. Assessments will become less frequent during the long-term follow-up period. Changes in tumor assessments (either PR or CR) must be confirmed by repeat assessments that should be performed ≥ 4 weeks after criteria for response are first met. See Section 8.2.2.3.

t. **Administer IV Fluids**: Patients should receive administration of 1 liter of normal saline IV with study treatment infusion on Day 1 of each cycle. In addition, consider administering 1 liter of normal saline IV when the patients return for clinic visits (ex. if the patient returns for PK draws on Days 3 and 5 of Cycle 1), anytime based on the patients need, or as clinically indicated. See Section 5.3.4.2.

u. **Prophylactic Acetaminophen/NSAIDS**: Patients will be premedicated with acetaminophen (eg, 650 mg every 6 hours) or NSAIDs (eg, ibuprofen 400 mg every 6 hours) on Day 1 of each cycle. In addition, administer acetaminophen or NSAIDs on Day 2 to 5 of each cycle.

v. **Drug Administration**: When administered on the same day, NKTR-214 will be administered first (30 ± 5 minutes) followed by pembrolizumab (30 ± 5 minutes). See Section 5.3.1. After NKTR-214 administration, flush the intravenous line with an appropriate amount of the same diluent used for dose preparation to ensure that the total dose is completely administered over the appropriate time. No delay is necessary between drug administrations after checking for stable vitals. Chemotherapy drugs will be administered after Pembrolizumab following local practice and labels.

w. **For Australia Only: Serum Cortisol Level**: The Belberry HREC requires that all study Investigators in Australia follow the current NCCN guidelines relating to the management of immune checkpoint inhibitor-related toxicities, specifically related to serum cortisol monitoring. Please refer to the current version of the above-mentioned guidelines (Thompson 2020) and ensure that compliance with the guidelines is documented in the patient source documentation. Serum cortisol monitoring should be performed in Cycles 1, 2, 3, and 4 only.

Abbreviations: CVA = cerebrovascular event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiography; EOT = End of Treatment; IV = intravenous; MUGA = multigated acquisition; NSAIDS = nonsteroidal anti-inflammatory drugs; PK = pharmacokinetic

2.0 INTRODUCTION

2.1 Background

2.1.1 NKTR-214 Mechanism of Action

Bempegaldesleukin (NKTR-214) is a prodrug of a conjugated cancer immunotherapy cytokine that exerts its biological activity by binding to the IL-2 receptor and subsequent activation of effector T cells. As a PEGylated human recombinant IL-2 molecule of aldesleukin with an average of six releasable polyethylene glycol (PEG) chains, NKTR-214 can be administered conveniently in the outpatient setting using an antibody-like dosing regimen. The polymer conjugation renders the cytokine initially inactive. Upon intravenous administration, the PEG chains slowly release to generate the active cytokine species (mainly 2-PEG-IL-2 and 1-PEG-IL-2) that have a peak plasma concentration 26 to 48 hours after infusion. The slow generation of the 2-PEG-IL-2 and 1 PEG-IL-2 significantly mitigates the rapid-onset, systemic cytokine-related toxicities associated with high dose IL-2.

The polymer conjugation of NKTR-214 promotes biased signaling through the IL-2 receptor beta gamma (IL-2Rβγ). Specifically, the location of the NKTR-214 PEG chains interferes with binding to the IL-2 alpha receptor subunit responsible for the undesirable effect of activating Tregs in the tumor while continuing to permit binding to the IL-2Rβγ (CD122) receptor. Upon infusion, NKTR-214 preferentially increases the proliferation, activation, and effector function of tumor antigen-specific CD8+ T cells and natural killer (NK) cells within the tumor microenvironment (TME) over expansion of unwanted intra-tumoral regulatory T cells (Tregs) that are activated through the IL-2 receptor alpha beta gamma (IL-2Rαβγ) (Charych 2016).

NKTR-214 also correspondingly promotes expression of PD-1 on the surface of CD8+ T cells and induction of a Type II interferon gene signature in the TME, driving cell surface expression of programmed cell death ligand 1 (PD-L1) on tumor cells (Diab 2017).

The immunological properties of NKTR-214 with the induction of tumor infiltrating lymphocytes and upregulation of the PD-1/PD-L1 axis makes NKTR-214 a potentially promising combination therapy for use with checkpoint inhibitors that target and inhibit the PD-1/PD-L1 pathway. Moreover, the safety profile of NKTR-214 does not overlap with that of checkpoint inhibitors, further supporting the use of NKTR-214 as a potentially complimentary combination partner with checkpoint inhibitors.

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/anti-programmed cell death ligand 1 (PD-L1) 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; not responsive to nivolumab) was treated with high-dose IL-2 (Brayer 2014). A larger experience from an observational clinical trial reported that patients with metastatic melanoma who received high-dose IL-2 and received either ipilimumab or an anti-PD-1 inhibitor experienced a differential increase in median overall survival, 15.8 vs 28.7 months, respectively. The 12-month survival rate was 64% for patients receiving ipilimumab post high-dose IL-2 compared with 97% for patients receiving an anti-PD-1 inhibitor, suggesting that these two checkpoint inhibitors do not have overlapping mechanisms of action and that IL-2 may enhance the curative potential of the anti-PD-1 inhibitor (Wong 2015).

In support of the hypothesis that IL-2 may have enhanced the curative potential of nivolumab/pembrolizumab, a recent report demonstrated that IL-12, which has been shown to induce tumor infiltrating lymphocytes and anti-tumor immunity similar to IL-2, appeared to prime response to anti-PD-1/PD-L1 inhibitors and demonstrated a clinical benefit rate of 75% (50% CR and 25% partial response [PR]) (Algazi 2016).

Further support comes from clinical data from ongoing clinical trial 16-214-02 (PIVOT-02; NCT02983045), in which the combination of NKTR-214 and an anti-PD-1 (nivolumab) has shown rapid tumor response in patients. These data are discussed in Section 2.1.4, which describes overall clinical experience with NKTR-214, and in Section 5.3.3, which details the rationale for the dose of NKTR-214 used in the present study.

2.1.4 Clinical Experience with NKTR-214

As of the data cutoff date (29 October 2019) for the NKTR-214 Investigator's Brochure, efficacy and safety data were available from two additional clinical studies of NKTR-214:

- EXCEL Study 15-214-01 (NCT02869295) (complete): A Phase 1/2, Open-label, Multicenter, Dose-Escalation and Dose Expansion Study of NKTR-214 in Subjects with Locally Advanced or Metastatic Solid Tumor Malignancies. This monotherapy study has completed enrollment and all patients have completed treatment.
- PIVOT-02 Study 16-214-02 (ongoing): 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.

Highlights of these studies are presented below; additional details on the clinical experience with NKTR-214 are provided in the NKTR-214 Investigator's Brochure.

2.1.4.1 Study 15-214-01 (EXCEL)

Study 15-214-01 (NCT02869295) was 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 EXCEL study (15-214-01) were 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 at or below the MTD, or to identify the recommended Phase 2 dose (RP2D). NKTR-214 was assessed in 28 patients across 5 dose cohorts in which NKTR-214 was administered at a dosing frequency of q3w at doses of 0.003, 0.006, 0.009, and 0.012 mg/kg, and at a dosing frequency of q2w at a dose of 0.006 mg/kg.

Enrollment in EXCEL (15-214-01) was closed after 28 patients were exposed to NKTR-214 in the dose-escalation phase in order to allow continued development of NKTR-214 in combination through other studies (final database lock 29 March 2018). While no objective responses were observed, 9 patients experienced tumor shrinkage between 1% and 30% and two patients, after progressing on multiple prior therapies, had durable SD > 1 year. One patient with metastatic melanoma, who was previously treated with ipilimumab and a BRAF inhibitor received 25 cycles of NKTR-214 and had durable SD for 18 months. A second patient with metastatic RCC, who had progressed on high dose IL-2 and was refractory to single agent OX40 and nivolumab, was treated with 19 cycles of NKTR-214 and had durable SD for 14 months. Given the biological properties of NKTR-214 and nivolumab these observations further supported the rationale for combining these two agents.

NKTR-214 monotherapy was generally well tolerated. NKTR-214 at a dose of 0.009 mg/kg administered every 3 weeks (q3w) was deemed the MTD by predefined dose limiting toxicity (DLT) criteria. At the 0.012 mg/kg dose level, 1 patient experienced DLTs of Grade 3 hypotension and syncope, which were rapidly reversed with intravenous fluids; this patient

continued on study and received 2 additional doses of NKTR-214 0.006 mg/kg and tolerated treatment well. Dosing of NKTR-214 at 0.006 mg/kg every 2 weeks (q2w) and q3w, as well as dosing at 0.003 and 0.009 mg/kg at q3w of NKTR-214 monotherapy were also deemed safe by the Safety Review Committee (SRC). One patient dosed at 0.009 mg/kg discontinued the study due to a serious adverse event (SAE) of Grade 3 infusion-related reaction (including diaphoresis, rash, shortness of breath, chest tightness, tingling in tongue, low blood pressure [47/44 mm Hg], and hyperglycemia). The reaction occurred following the first dose of NKTR-214 and resolved with treatment (oxygen, epinephrine, and antihistamines). This patient had a prior history of an infusion-related reaction to a previously administered immuno-oncology agent.

The most common treatment-related AEs included fatigue (71.4%), flu-like symptoms (67.9%), pruritus (64.3%), hypotension (57.1%), rash (50.0%), decreased appetite (46.4%), and arthralgia or cough (each 32.1%). Such treatment-related AEs as flu-like symptoms, rash and pruritus were generally mild to moderate in severity, monitorable, manageable, and transient. These low-grade cytokine-related AEs generally occurred 3 - 4 days after dosing and corresponded to the time of peak plasma concentration of the active cytokines. The flu-like symptoms were managed with acetaminophen and NSAIDs and the cases of rash/pruritus were either self-limiting or treated with antihistamines (steroids were administered for occasional patients who had severe rash/pruritus). Six of 28 patients reported Grade 3 treatment-related AEs, which included hypotension, abdominal pain, infusion-related reaction, headache, and syncope; Cases of Grade 3 hypotension were rapidly reversed with IV fluids. To mitigate the risk of hypotension (a known adverse event (AE) associated with both IL-2 and engineered cytokines), management guidelines were implemented and included the following recommendations:

- Withholding antihypertensive therapy and drugs with hypotensive properties, prior to administration of NKTR-214.
- Administration of at least 1 L of IV fluids at the time of each NKTR-214 administration (Day 1).
- Maintaining adequate oral fluid intake, particularly during the first 4 days postdose.
- Avoiding activities that could lead to dehydration (eg, physically strenuous activity) or vasodilation (eg, 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 successfully reduced.

Hydration guidelines to help manage the risk of hypotension are provided in detail in Section 5.3.4.2.

Other than one case of hypothyroidism reported in this monotherapy trial, no clinically confirmed cases of immune-mediated AEs (as seen with immune checkpoint inhibitors) or

capillary leak syndrome (as observed with other IL-2 therapy) have been reported in NKTR-214 monotherapy study. No anti-drug antibodies (ADAs) to NKTR-214 or IL-2 were detected in any of the 28 treated patients. No Grade 4 treatment-related TEAEs or treatment-related deaths were reported on the study.

2.1.4.2 Study 16-214-02 (PIVOT-02)

Study 16-214-02 is a Phase 1/2, open-label, multicenter study of the combination of NKTR-214 with nivolumab or the combination of NKTR-214, nivolumab, and other anti-cancer therapies in patients with select locally advanced or metastatic solid tumor malignancies. Phase 1 (dose escalation cohort) enrolled patients with advanced or metastatic melanoma, RCC, or non-small cell lung cancer (NSCLC). In Phase 2 (dose expansion cohort), additional tumor types were added: breast cancer, urothelial carcinoma, and gastrointestinal malignancies. Part 3 (triplet dose escalation cohort) assesses schedules for NKTR-214 in combination with nivolumab and ipilimumab to establish RP2Ds for concurrent and staggered dosing schedules. Part 4 studies the RP2D for each respective tumor type. The objectives of the study are to evaluate the safety and tolerability of NKTR-214 to determine the MTD and/or the RP2D as well as to assess the ORR at the RP2D.

The doses studied in the dose escalation part of the study were NKTR-214 0.003 or 0.006 mg/kg q2w with nivolumab 240 mg q2w; NKTR-214 0.006 mg/kg q3w with nivolumab either 240 mg q2w or 360 mg q3w; and NKTR-214 0.009 mg/kg q3w with nivolumab 360 mg q3w. The dose escalation portion of this study (Part 1) has been completed.

Based on the findings from the NKTR-214 monotherapy study (EXCEL; 15-214-01; see Section 2.1.4.1) and findings from the dose-escalation part of the PIVOT-02 study, the RP2D of NKTR-214 in combination with nivolumab 360 mg q3w was determined to be 0.006 mg/kg. The rationale for this dose is further detailed in Section 5.3.3.

The doses studied in the expansion portion part of the study have been NKTR-214 0.006 mg/kg q3w plus nivolumab 360 mg q3w plus ipilimumab 1 mg/kg q6w (RCC/NSCLC); 4 doses of NKTR-214 0.006 mg/kg q3w plus nivolumab 1 mg/kg q3w plus ipilimumab 3 mg/kg q3w; then continue with NKTR-214 0.006 mg/kg plus nivolumab 360 mg (urothelial carcinoma/melanoma); 4 doses of NKTR-214 0.006 mg/kg q3w plus nivolumab 3 mg/kg q3w plus ipilimumab 1 mg/kg q3w; then continue with NKTR-214 0.006 mg/kg plus nivolumab 360 mg (RCC/melanoma).

As of the data cutoff date (29 October 2019) for the NKTR-214 Investigator's Brochure, tumor response data were available for 37 patients in the dose escalation phase of the study; among these patients 21 (56.8%) had CR or PR.

In the dose expansion phase of the study patients received treatment with the RP2D:

- In 1L RCC patients who met the prespecified efficacy parameters a 46% (12 of 26 patients) objective response rate (ORR) was noted. Responses were seen in both PD-L1 positive (29%, 2 of 7 patients) and PD-L1 negative (53%, 9 of 17 patients) (Diab 2018a; 29 May 2018 cutoff).
- In urothelial carcinoma patients, a 48% (13 of 27 patients) ORR was noted with a 19% complete response rate. Responses were seen in both PD-L1 positive and PD-L1 negative expression on tumor populations with an ORR of 50% in the PD-L1 positive population (6 of 12 patients) and 43% in the PD-L1 negative population (5 of 11 patients) (Siefker-Radtke 2019; 03 Dec 2018 data cutoff).
- In 1L melanoma patients who met the prespecified efficacy parameters, a 53% (20 of 38 patients) ORR was seen via independent central radiology review with a 34% (13 of 38 patients) CR rate. Responses were seen in both the PD-L1 positive (defined as PD-L1 expression ≥ 1% on tumor cells) and PD-L1 negative (defined as < 1% PD-L1 expression on tumor cells) populations with an ORR of 64% in the PD-L1 positive population (14 of 22 patients) and 39% in the PD-L1 negative population (5 of 13 patients) (Diab 2019; 25 Sep 2019 data cutoff).
- In mTNBC patients who met the prespecified efficacy parameters, 13.2% (5 of 38 patients) ORR was noted. Responses were seen in both PD-L1 positive and PD-L1 negative populations with an ORR of 16.7% in the PD-L1 positive population (2 of 12 patients) and 13.6% in the PD-L1 negative population (3 of 22 patients) (Tolaney 2019; 01 Jul 2019 data cutoff).

The most frequently reported TEAEs were fatigue (294 of 541 patients, 54.3%), pyrexia (274 of 541 patients, 50.6%), nausea (227 of 541 patients, 42.0%) pruritus (215 of 541 patients, 39.7%), decreased appetite (203 of 541 patients, 37.5%), diarrhoea (168 of 541 patients, 31.1%) and influenza-like illness (168 of 541 patients, 31.1%).

The most frequently reported treatment-related TEAEs were fatigue (267 of 541 patients, 49.4%), pyrexia (245 of 541 patients, 45.3%), pruritus (200 of 541 patients, 37.0%), nausea (178 of 541 patients, 32.9%) and influenza-like illness (165 of 541 patients, 30.5%). The most frequently reported TEAEs assessed as related in the 488 patient doublet group were fatigue (47.3%), pyrexia (44.3%), pruritus (35.7%), nausea (29.7%), influenza-like illness (26.8%), decreased appetite (26.4%), chills (26.0%), and rash (25.8%). For the 43 triplet patients, the most frequently reported TEAEs assessed as related were fatigue (79.1%), influenza-like illness (72.1%), nausea (60.5%), pruritus or diarrhoea (58.1%), pyrexia (55.8%), rash maculo-papular (53.5%), decreased appetite (46.5%), vomiting (39.5%), chills or hypothyroidism (37.2%), oedema peripheral (34.9%), arthralgia (32.6%), and cough (30.2%). Among the doublet plus other anti-cancer study drug patients, 7 of 10 experienced nausea assessed as related, 5 pyrexia, 4 hypotension, and 3 alopecia, neutropenia, constipation, influenza-like illness, dizziness, vomiting, or decreased appetite.

As of the 28 October 2019 database cutoff date, 44.9% of patients reported SAEs. The most frequently experienced SAEs were pyrexia by 19 of 541 patients (3.5%), dyspnea and hypotension by 16 of 541 patients (each: 3.0%), and hyponatremia by 11 of 541 patients (2.0%). In the doublet (NKTR-214 plus nivolumab) cohort 218 of 488 patients (44.7%) experienced an SAE. The most frequently reported SAEs were pyrexia (18 patients of 488, 3.7%), dyspnea or hypotension (each: 14, 2.9%) and hyponatraemia (10, 2.0%). In the triplet cohort (NKTR-214 plus nivolumab plus ipilimumab), 21 of 43 patients (48.8%) experienced SAEs. The most frequently reported were cerebrovascular accident in 3 patients (7.0%), acute kidney injury, embolism, adrenal insufficiency, or enterocolitis (each: 2 patients, 4.7%). Four of the 10 patients in the doublet plus other anti-cancer drug group experienced SAEs: 2 hypotension, and 1 each dyspnea, pneumonia, embolic stroke, or confusional state.

A total of 102 patients of 541 (18.9%) reported SAEs that were considered related to any study treatment. In the doublet cohort, 84 of 488 patients (17.2%) experienced SAEs assessed as related. The most frequently reported were pyrexia (15 patients, 3.1%), hypotension (10, 2.0%), and pneumonitis (5, 1.0%). In the triplet cohort, 16 of 43 patients (37.2%) experienced SAEs assessed as related: cerebrovascular accident (3 patients of 43, 7.0%), acute kidney injury, adrenal insufficiency, or enterocolitis (each: 2 patients, 4.7%), and 1 patient each (2.3%) experienced thyroiditis, papilledema, influenza-like illness, hypothyroidism, hypophysitis, eosinophilia, diarrhoea, colitis, hyperthyroidism, hyponatraemia, atrial fibrillation, or pneumonitis. Two of the 10 patients in the doublet plus other anti-cancer drug cohort experienced an SAE of hypotension assessed as related.

Twelve (2.2% of 541 patients) Grade 5 events have been reported. Nine patients in the doublet therapy regimen experienced Grade 5 events: 3 pneumonitis, 1 cardiac arrest, and 1 acute respiratory failure (assessed as related to one or both), and 1 cardio-respiratory arrest, 1 cardiac arrest, 1 large intestine perforation, and 1 respiratory failure (all unrelated). In the doublet plus other anti-cancer drug group 1 patient experienced embolic stroke (unrelated). In the triplet therapy regimen, 2 patients experienced Grade 5 events: adrenal insufficiency and cerebrovascular accident; both were assessed as related to all 3 drugs.

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

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

Serious events of cerebrovascular accident (CVA), including 1 fatal event, were observed in patients who have received NKTR-214 in the triplet combination with nivolumab and ipilimumab and in the doublet combination with nivolumab. A comprehensive search (data cutoff 21 June 2019) found 3 of 43 patients (7%) who received triplet therapy in Study 16−214−02 (PIVOT-02) to have CVA events, all of which were considered by the Investigator to be related to treatment with NKTR-214, nivolumab, and ipilimumab. Eight of 478 patients (1.7%) who received doublet immunotherapy (NKTR-214 and nivolumab) in Study 16-214-02 were determined to have CVA events that were confirmed by the neurology

consultants. 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%). Between 21 June 2019 and 28 October 2019, a 71-year-old male with urothelial carcinoma on doublet therapy reported 1 Grade 2 SAE of cerebrovascular accident which resulted in dose delay and was reported as not related to study therapy due to the presence of multiple risk factors as confounders. One 66-year-old male patient with NSCLC on doublet therapy plus chemotherapy reported Grade 5 embolic stroke.

In summary, a total of 9 patients out of 488 patients (1.8%) in NKTR-214 plus nivolumab doublet therapy reported a CVA event. One patient and 3 patients who received doublet therapy plus chemotherapy and triplet therapy, respectively, reported a CVA event.

The relationship of these events to the triplet and doublet combinations is unclear. Based on these events and a comprehensive assessment of CVA across all NKTR-214 clinical studies, CVA has been escalated to an adverse event of special interest (AESI) and mitigations have been put in place to reduce the risk of CVA. These mitigations include implementation of a cerebrovascular accident adverse event management algorithm (Appendix 2) and updates to the exclusion criteria, renal function and hydration assessment, hydration guidelines, concomitant and prohibited medications, dose modification guidelines, and discontinuation criteria. Additional information on the clinical safety and risk of CVA is found in the NKTR-214 Investigator's Brochure.

2.1.5 Pembrolizumab Safety Summary

See the pembrolizumab prescribing information.

2.1.6 Rationale for Dose Optimization Cohorts

The dose optimization cohorts have been added to investigate the safety profile and MTD/RP2D of NKTR-214 in combination with pembrolizumab in locally advanced or metastatic solid tumors (see Section 5.3.2.1).

2.1.7 Rationale for Dose Expansion Cohorts 2, 3, 4, and 5

For 1L NSCLC patients with a percentage of tumor cells expressing PD-L1 ≥ 1%, pembrolizumab has become a standard of care in the United States (US). In NSCLC patients with tumors that do not express PD-L1 (< 1%), pembrolizumab monotherapy data are limited. Given that treatment with NKTR-214 can increase PD-L1 expression on T cells in the blood and tumor, and increase the number of tumor-infiltrating lymphocytes, the addition of NKTR-214 is expected to improve the effectiveness of pembrolizumab in this population.

Based on its mechanism of action, NKTR-214 in combination with pembrolizumab may improve response rates in first-line NSCLC patients, especially with low or negative PD-L1 expression. Thus, treatment with NKTR-214 at a dose of 0.006 mg/kg (Cohort 2) in combination with pembrolizumab was added to this protocol to evaluate efficacy in first-line NSCLC patients

regardless of PD-L1 expression. In Amendment 5, the dose of NKTR-214 at 0.010 mg/kg was tested in 7 patients in the dose optimization cohort. The first 6 patients were evaluated by the SRC for safety in this cohort. No DLTs were seen during the DLT period. The AEs that were related to NKTR-214 matched the expected toxicity profile. No dose delays or dose modifications were noted in the 6 patients during the DLT period.

In patients with previously untreated metastatic, squamous cell lung cancer, the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel resulted in significantly longer overall survival and progression-free survival than chemotherapy alone (Paz-Ares 2018). In patients with previously untreated metastatic, nonsquamous NSCLC, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and progression-free survival than chemotherapy alone (Gandhi 2018). Given its mechanism of action, NKTR-214 in combination with pembrolizumab may improve response rates in both squamous cell lung cancer and nonsquamous NSCLC patients (Cohorts 4 and 5).

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 dose-limiting toxicities of aldesleukin, ie, those necessitating in-hospital administration, appears to have been realized with NKTR-214 at the doses tested. The safety profile of pembrolizumab is well characterized and manageable, including regimens where it is administered in combination with other immuno-oncology products. Clinical experience with the recommended phase 2 dose (RP2D) of NKTR-214 (0.006 mg/kg) in combination with nivolumab showed improvement in therapeutic response (ie, ORR and DCR) compared with either agent given alone. The conversion of PD-L1 (–) to PD-L1 (+) in tumor biopsies is associated with clinical benefit and rapid activation of the immune system (ie, increased lymphocyte proliferation in blood and increased CD8 T cells in tumors), which is consistent and maintained with successive treatment cycles has also been observed with NKTR-214 in combination with nivolumab. Furthermore, NKTR-214 in combination with nivolumab or pembrolizumab has so far demonstrated an acceptable safety profile in clinical studies. Thus, the potential benefit of combination therapy appears to outweigh the known risks of these agents and warrants continued 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.

3.0 STUDY OBJECTIVES

3.1 Primary Objectives: Dose Optimization or Dose Expansion Cohorts

The primary objectives in the dose optimization cohorts are:

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

The primary objective in all the dose expansion cohorts is:

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

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

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

- To evaluate safety and tolerability of NKTR-214 plus pembrolizumab with or without systemic chemotherapy in patients with untreated NSCLC (dose expansion only).
- To assess the preliminary efficacy (per BICR) of NKTR-214 plus pembrolizumab with or without systemic chemotherapy:
    - objective response rate (ORR) by RECIST 1.1 (dose optimization only)
    - duration of response (DOR) by RECIST 1.1
    - clinical benefit rate (CBR) by RECIST 1.1
    - time to response (TTR) by RECIST 1.1
    - progression-free survival (PFS) by RECIST 1.1
    - overall survival (OS)

[redacted]

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

A patient must meet all of the following criteria:

1. Provide written, informed consent to participate in the study and follow the study procedures.
2. Age 18 years or older at the time of signing the informed consent form (ICF).
3. Life expectancy > 12 weeks from the time of enrollment as determined by the Investigator.
4. In the dose optimization cohorts, patients may have received no more than 1 prior line of systemic therapy for metastatic cancer. 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 in a non-palliative setting and is stopped for progression of disease.
5. Patients must have a minimum of 6 months of response to any non-palliative cancer-directed treatment.
6. Prior IL-2 therapy is allowed for patients in the dose optimization cohorts who have completed therapy, and who have reported no severe ADRs or had all ADRs completely resolved. Prior IL-2 therapy is not allowed for patients in the dose expansion cohorts.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Measurable disease per RECIST 1.1.
9. Adequate organ function, as defined in Table 5, within 28 days of treatment initiation.

Table 5: Definitions of Adequate Organ Function (Inclusion Criteria)

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1500/μL (after at least 7 days without growth factor support).
Platelet count	≥ 100×10^3/μL (no transfusions allowed within 7 days of Day 1, Cycle 1)
Hemoglobin	≥ 9.0 g/dL (no transfusions allowed within 7 days of Day 1, Cycle 1)
Renal	
Serum creatinine	≤ 2 mg/dL Cohorts 4 and 5: creatinine clearance (CLcr) ≥ 45 mL/min

Table 5: Definitions of Adequate Organ Function (Inclusion Criteria) (Contd)

System	Laboratory Value	
Hepatic		
Aspartate aminotransferase (AST) and alanine transaminase (ALT)	≤ 3 × upper limit of normal (ULN).	
Total bilirubin	Cohorts 1, 2, 3: Within normal limits (total bilirubin ≤ 2 × ULN if associated with hepatobiliary metastases or Gilbert's syndrome). Cohorts 4, 5: ≤ 1.5 x ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN	
Pancreatic		
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.	
Coagulation (Cohorts 4 and 5)		
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)	≤1.5 x ULN unless the subject is receiving anticoagulant therapy ≤1.5 x ULN unless the subject is receiving anticoagulant therapy	

10. A documented left ventricular ejection fraction (LVEF) > 45% using standard echocardiogram (ECHO) or multigated acquisition (MUGA) scan within 90 days prior to Cycle 1 Day 1.

11. Oxygen saturation ≥ 90% on room air for all indications.

12. Clinically significant toxic effect(s) of the most recent 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) may be enrolled provided that clinical symptoms are adequately controlled and the daily dose is 10 mg or less of prednisone or equivalent. Patients with hypothyroidism that is stable on hormone replacement therapy may also be enrolled. 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.

13. Women of childbearing potential (WCBP) must commit to the use of highly effective methods of birth control during study participation for 4 months following the last dose of all study drug(s). Acceptable methods are those that, alone or in combination, result in a low failure rate (< 1% per year), such as surgical sterilization, an intrauterine device, or hormonal contraception in combination with a barrier method. Abstinence is acceptable if this is the preferred contraception. Women of Childbearing Potential who are continuously not heterosexually active are exempt from contraceptive requirements, but still must undergo pregnancy testing as scheduled. Detail is provided in Appendix 3.

14. Male patients who are sexually active with WCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) and 3 months after NKTR-214 and/or pembrolizumab treatment completion. In addition, male patients must be willing to refrain from sperm donation during this time (Appendix 3).

15. Patients with hypertension must be on ≤ 2 antihypertensive medications and without change for the 14 days prior to randomization. Screening blood pressure must be systolic < 150 mm Hg and < 90 mm Hg for diastolic blood pressure.

    - For France only: screening blood pressure must be systolic < 140 mm Hg and < 90 mm Hg for diastolic blood pressure.

16. A brain MRI at Screening is required for all patients with metastatic NSCLC, and for patients with other tumor types who have known brain metastasis.

17. Patients with brain metastases are eligible if all the criteria below are fulfilled:

    a. Brain metastases must be treated at least 2 weeks prior to enrollment.

    b. Brain imaging after treatment and within the screening period must demonstrate no new or progressing brain metastases.

    c. No requirement for systemic corticosteroids > 10 mg/day prednisone equivalents at therapy initiation. Stable doses of anticonvulsants are allowed.

    d. No clinically significant symptoms associated with brain metastases.

18. A tumor tissue sample is required for all patients. Acceptable samples include archival tissue obtained no more than 12 months prior to enrollment if the patient has not received systemic treatment between the time of biopsy/resection and enrollment. Otherwise, a fresh tumor biopsy taken during screening is required.

19. For France only: enrolled patients must be affiliated to a Social Security System.

The following additional inclusion criteria are for the dose optimization cohorts (see Section 4.1.1) or dose expansion cohort (see Section 4.1.2) only.

4.1.1 Dose Optimization Cohorts (Cohorts 1a and 1b)

The tumor types included in the dose optimization cohorts of the study are shown in Table 6.

Table 6: Tumor Types to be Included in Dose Optimization Cohorts (NKTR-214 and Pembrolizumab)

Tumor Type	Line of Treatment in Metastatic Setting	PD-L1 Status
Melanoma	1st and 2nd	Any
Non-small cell lung cancer	1st and 2nd	Any
Urothelial carcinoma	1st and 2nd	Any
Head and neck squamous cell cancer	1st and 2nd	Any
Hepatocellular carcinoma	1st and 2nd	Any

20. 1L and 2L Melanoma

    a. Histologically confirmed diagnosis of Stage IV (metastatic) melanoma.

21. 1L and 2L Non-small Cell Lung Cancer (NSCLC)

    a. Histologically confirmed diagnosis of Stage IV NSCLC.

    b. Patients with actionable mutations with approved targeted therapy in NSCLC are excluded. Testing for mutations should be performed per standard of care.

22. 1L and 2L Urothelial Carcinoma

    a. Histologically confirmed diagnosis of metastatic urothelial carcinoma.

23. 1L and 2L Head and Neck Squamous Cell Carcinoma (HNSCC)

    a. Histologically confirmed diagnosis of metastatic HNSCC

24. 1L and 2L Hepatocellular Carcinoma (HCC)

    a. Histologically confirmed diagnosis of metastatic HCC.

4.1.2 Dose Expansion Cohorts (Cohorts 2, 3, 4, and 5)

25. 1L Non-Small Cell Lung Cancer (Cohorts 2, 3, 4, and 5)

- Histologically confirmed diagnosis of Stage IV NSCLC.

- Tumor tissue sample is required to be submitted to the central lab for all patients prior to enrollment. Acceptable samples include archival tissue obtained no more than 12 months prior to enrollment if the patient has not received systemic treatment between the time of biopsy/resection and enrollment. Otherwise, a fresh tumor biopsy taken during screening is required. A tracking number confirming shipment of the sample to the central laboratory must be supplied prior to Cycle 1 Day 1. Within each subgroup, this is:
    - PD-L1 negative (PD-L1 < 1%; Cohort 2.1): 20 response-evaluable patients
    - PD-L1 low/intermediate (PD-L1 1% to 49%; Cohort 2.2): 18 response-evaluable patients
    - PD-L1 highly positive (PD-L1 ≥ 50%; Cohort 2.3): 20 response-evaluable patients
    - For France only: patients in subgroup PD-L1 < 50% (Cohorts 2.1, 2.2) will be excluded. Eligibility for PD-L1 status can be determined with a local or central PD-L1 test.
- Patients with actionable mutations with approved targeted therapy in NSCLC are excluded. Testing for mutations should be performed per standard of care
- Must not have received anti-cancer therapy for treatment of metastatic lung cancer.
- Must not have received prior immunotherapy.

4.2 Exclusion Criteria

A patient will be excluded for any of the following criteria:

1. Use of an investigational agent or an investigational device within 28 days prior to enrollment.

2. Women who are pregnant or breastfeeding.

3. Patients who have an active, autoimmune disease. Exceptions include patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders not requiring systemic treatment, or autoimmune conditions not expected to recur.

4. History of allergy or hypersensitivity to study drug components.

5. Prior malignancy within the previous 3 years. Exceptions include non-melanoma skin cancer and carcinoma in situ, treated with curative intent, with minimal risk of recurrence or requiring therapy during study participation. Patients with prostate cancer are allowed if one of the following criteria is met: Stage T2N0M0 or lower; Gleason score ≤ 3 + 4, and prostate-specific antigen (PSA) below lower limit of normal by local laboratory.

6. Patients in the dose expansion cohorts must not have received prior immunotherapy or IL-2 therapy.

7. Chronic systemic corticosteroid at > 10 mg prednisone or equivalent or other immunosuppressive agents. Patient on inhaled steroids for asthma or local steroid injections or topical steroids are allowed.

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

9. Surgery or radiotherapy within 14 days of enrollment. Patients who had surgery or radiotherapy outside of 14 days must have recovered from associated complications and toxicities.

10. For Dose Optimization Cohort 1 only: Chemotherapy or biological therapy within 28 days of enrollment. Targeted therapy (eg, tyrosine kinase inhibitors) within 14 days of enrollment. Patients with ongoing AEs related to prior cancer therapies will be excluded.

11. For Dose Expansion Cohorts: Patients with ongoing AEs related to prior cancer therapies will be excluded.

12. Active infection requiring systemic therapy/ Active hepatitis B virus (HBV) infection (eg, positive hepatitis B surface antigen [HBsAg]) or hepatitis C virus (HCV) infection (eg, positive HCV ribonucleic acid [RNA]).

13. Known immunodeficiency or active human immunodeficiency virus (HIV-1/2 antibodies).

14. Known active SARS-CoV2 infection with confirmed test report.

15. For France only: received a live vaccine within 30 days prior to the first dose of the study.

16. For France only: known history of active tuberculosis (TB: Bacillus tuberculosis).

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

18. Known cardiovascular history, including cerebrovascular disease within 12 months of 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. Cerebrovascular accident (CVA) or transient ischemic attack (TIA).
    e. History of pulmonary embolism (PE), deep vein thrombosis (DVT), or venous or non-CVA/TIA arterial thromboembolic event within 3 months prior to enrollment.

- Patients with a history of a venous or arterial thromboembolic event must be asymptomatic prior to enrollment and must be receiving a stable regimen of therapeutic anticoagulation (low molecular weight heparin [LMWH] or direct oral anticoagulation [DOAC]) or had received appropriate treatment as indicated by the regional clinical guidelines. Additionally:
- Use of coumadin is permitted; however, therapeutic dosing should target a specific international normalized ratio (INR) stable for at least 4 weeks prior to enrollment. NKTR-214 has the potential to down-regulate metabolizing enzymes for coumadin for approximately 1 week after administration of each dose of NKTR-214. Due to the possibility of drug-drug interactions between coumadin and NKTR-214, frequent monitoring of INR and ongoing consideration of dose adjustments are warranted throughout the patient's participation on study.

19. Current 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 of adverse events while participating in study.

5.0 TREATMENT PLAN

5.1 Overview

This is a Phase 1/2, open-label, multicenter, study of NKTR-214 in combination with pembrolizumab with or without systemic chemotherapy in patients with metastatic solid tumors. The dose optimization cohorts (Cohorts 1a and 1b) will include first- and second-line (1L and 2L) melanoma, non-small cell lung carcinoma (NSCLC), urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), and hepatocellular carcinoma (HCC). The dose optimization Cohort 1a will include patients enrolled in the 3 + 3 dose optimization cohort and the dose optimization Cohort 1b will include patients enrolled in the step-up dose optimization cohort. The dose expansion cohorts (Cohorts 2, 3, 4, and 5) will include first-line NSCLC patients, first-line, nonsquamous NSCSC patients, and first-line squamous cell lung cancer patients.

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

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

All procedures are outlined in the Schedule of Events (Section 1.1).

5.2 Screening Period

The screening period is 28 days. Patients must provide written informed consent before starting screening and any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. The screening period ends on the day before Cycle 1 Day 1. Assessments done on Cycle 1 Day 1 prior to dosing are considered Cycle 1 Day 1 assessments and not screening assessments. Patients may be rescreened up to 1 time at the discretion of the Investigator.

Dose Expansion Cohorts 2, 3, 4, and 5 only: A tumor tissue sample is required to be submitted to the central lab for all patients prior to enrollment. Acceptable samples include archival tissue obtained no more than 12 months prior to enrollment if the patient has not received systemic treatment between the time of biopsy/resection and enrollment. Otherwise, a fresh tumor biopsy

taken during screening is required. A tracking number confirming shipment of the sample to the central laboratory must be supplied prior to Cycle 1 Day 1. This will allow for prompt PD-L1 testing and results to ensure patient's timely allocation to appropriate PD-L1 sub-cohort (Cohorts 2.1, 2.2, 2.3, 3.1, 3.2, 3.3, 4.1, 4.2, 4.3, 5.1, 5.2, and 5.3). Sub-cohorts may be opened and closed to further accrual as determined by various factors, such as the number of response-evaluable patients enrolled within each sub-cohort.

5.3 Treatment Period

Patients will be treated up to 2 years (or a maximum of 34 treatment cycles, whichever is sooner) until disease progression, death, unacceptable toxicity, symptomatic deterioration, lost to follow up, the Investigator decides to discontinue treatment, the patient decides to discontinue treatment or withdraw consent, or Nektar Therapeutics decides to terminate the trial.

Patients with progressive disease (PD) per RECIST 1.1 may continue study treatment if the Investigator considers it safe and in the best interest of the patient. See Section 5.3.6 for treatment beyond progression. Patients with a PR or stable disease (SD) will continue to receive study treatment until, disease progression (by investigator), or intolerability to therapy. The Investigator may continue treating patients with a confirmed CR, for a maximum treatment of 2 years from Cycle 1 Day 1.

5.3.1 Administration of Study Drug(s)

Each patient's NKTR-214 dose will be determined by the NKTR-214 dose optimization or dose expansion schema and the patient's weight in kilograms (Section 5.3.2). The patient's weight in kilograms will be determined on Day 1 before the start of each cycle; for weight changes of ± 10% from baseline, recalculation of dose is not required. When administered on the same day, NKTR-214 will be administered first (30 ± 5 minutes) followed by pembrolizumab (30 ± 5 minutes). After NKTR-214 administration and before pembrolizumab administration, flush the intravenous line with an appropriate amount of the same diluent used for dose preparation to ensure that the total dose is completely administered over the appropriate time. No delay is necessary between the two drug administrations, after checking for stable vital signs.

5.3.1.1 Dose Optimization Cohorts (Cohorts 1a and 1b)

Study Drug Administration - 3 + 3 Dosing (Cohort 1a) Schema

- NKTR-214 will be administered IV over 30 (± 5) minutes at a starting dose of 0.008 mg/kg. Please refer to the Pharmacy Manual for additional details for study drug administration.
    - Pembrolizumab will be dosed as per the Pharmacy Manual.

Study Drug Administration - Step-up Dosing (Cohort 1b) Schema

- NKTR-214 will be administered IV over 30 (± 5) minutes starting at the previously tolerated dose established in the 3 + 3 dosing schema as determined by the Safety Review Committee (SRC) for the step-up dosing schema. This dose may increase at each cycle for individual patients at increments of 0.002 mg/kg per the dose optimization schema in Figure 2. Please refer to the Pharmacy Manual for additional details for study drug administration.
  - Pembrolizumab will be dosed as per the Pharmacy Manual.

5.3.1.2 Dose Expansion Cohorts 2 and 3

- NKTR-214 will be administered q3w IV over 30 (± 5) minutes at a starting dose of 0.006 mg/kg in Cohort 2 (or 0.010 mg/kg in Cohort 3). Additional patients in the cohort may receive the dose as established by the dose optimization cohorts. Please refer to the Pharmacy Manual for additional details for study drug administration.
  - NKTR-214 will be dosed first, followed by pembrolizumab.
  - Pembrolizumab will be dosed as per the Pharmacy Manual. Pembrolizumab will be administered as a 30-minute IV infusion q3w.

5.3.1.3 Dose Expansion Cohort 4

- Cohort 4 will use the NKTR-214 dose administered in Cohort 2 (or Cohort 3) following review of efficacy and safety data. Please refer to the Pharmacy Manual for additional details for study drug administration.
  - NKTR-214 will be dosed first, followed by pembrolizumab, followed by chemotherapy.
  - Pembrolizumab will be dosed as per the Pharmacy Manual. Pembrolizumab will be administered as a 30-minute IV infusion q3w.
  - In Cohort 4, NKTR-214 will be dosed in combination with pembrolizumab and either cisplatin, or carboplatin and pemetrexed, per investigator discretion. Cisplatin, carboplatin, and pemetrexed will be dosed per the Pharmacy Manual. Pemetrexed 500 mg/m^2 will be administered as an IV infusion for 4 cycles followed by maintenance dose given every 3 weeks per local practice and label. Five doses of folic acid (each ranging from 350 µg to 1000 µg) should be taken during the 7 days preceding the first dose of pemetrexed and folic acid must continue during the full course of chemotherapy and for 21 days after the last dose of pemetrexed. Vitamin B12 1000 µg IM injection must be given in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B-12 injections maybe given on the same day as pemetrexed administration. Dexamethasone prophylaxis 4 mg must be taken on the day before, day of, and the day after pemetrexed administration.
  - Cisplatin 75 mg/m^2 will be administered as an IV infusion per local practice and labels for 4 cycles given every 3 weeks approximately 30 minutes after the pemetrexed infusion. It should be immediately preceded and followed by hydration procedures and administered according to local practice and labels.

- Carboplatin AUC 5 using Calvert formula will be administered as an IV infusion over 15 to 60 minutes for 4 cycles given every 3 weeks immediately after pemetrexed as per local practice and label. All subjects should be premedicated according to the approved product label and/or standard practice. The estimated GFR used in the Calvert formula should not exceed 125 mL/min. Maximum carboplatin dose should not exceed 750 mg.
- CALVERT formula: target AUC * (CLcr + 25)

5.3.1.4 Dose Expansion Cohort 5

- Cohort 5 will use the NKTR-214 dose administered in Cohort 2 (or Cohort 3) following review of efficacy and safety data. Please refer to the Pharmacy Manual for additional details for study drug administration.
  - NKTR-214 will be dosed first, followed by pembrolizumab, followed by chemotherapy.
  - Pembrolizumab will be dosed as per the Pharmacy Manual. Pembrolizumab will be administered as a 30-minute IV infusion q3w.
  - In Cohort 5, NKTR-214 will be dosed in combination with pembrolizumab and carboplatin and either nab-paclitaxel or paclitaxel, per investigator discretion. Nab-paclitaxel and paclitaxel will be dosed per local practice and label. Paclitaxel 200 mg/m^2 will be administered as an IV infusion over 3 hours q3w for 4 cycles. All subjects should be premedicated with oral or intravenous steroid and antihistamines according to the approved product label and/or standard practice.
  - Additional premedications should be administered as per local practice and label. Nab-paclitaxel will be administered at 100 mg/m^2 as an IV infusion over 30 minutes for 4 cycles as per local practice and label. Subjects will be dosed on Day 1, 8, and 15 of each q3w cycle.
  - Paclitaxel and nab-paclitaxel should be completely administered before initiating carboplatin dose. Carboplatin AUC 5mg/ml/min will be administered as an IV infusion over 15 to 60 minutes for 4 cycles given every 3 weeks immediately after pemetrexed as per local practice and label. All subjects should be premedicated according to local practice and label.

5.3.2 Dosing Schema: Dose Optimization and Dose Expansion Cohorts

5.3.2.1 Dose Optimization Cohorts (Cohorts 1a and 1b)

Patients enrolled in the 3 + 3 dose optimization schema (Cohort 1a) will start NKTR-214 at a dose of 0.008 mg/kg q3w with pembrolizumab. Patients enrolled in the step-up dose optimization schema (Cohort 1b) will start NKTR-214 q3w with pembrolizumab at the previously tolerated dose established in the 3 + 3 dose optimization schema as determined by the SRC. Doses will be increased in 0.002 mg/kg increments for the dose optimization cohorts. The risk mitigation measures for hypotension described in Section 5.3.4, such as hydration guidelines, have been found adequate to limit severity and frequency and have been implemented across the NKTR-214 studies following the EXCEL Study. Based on the adequacy of these

guidelines in managing hypotension, the Sponsor has moved forward with investigating doses of NKTR-214 higher than 0.009 mg/kg in the dose optimization scheme.

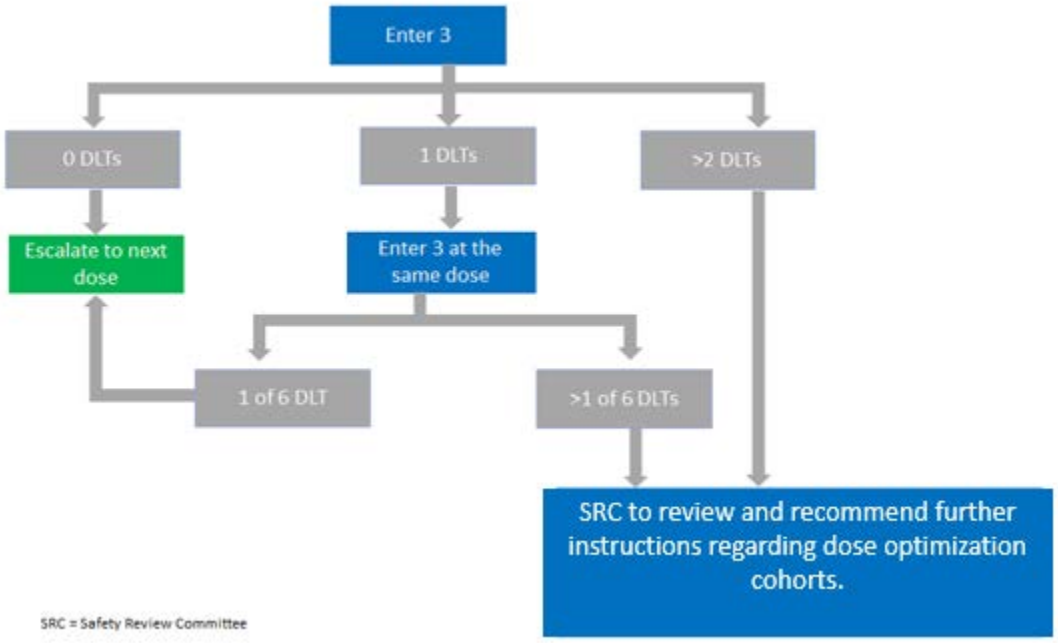
For dose optimization cohorts, the SRC will decide the following:

- Dose escalation to the next dose level.
- 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 pembrolizumab at higher doses and different dose schedules to assess the benefit/risk profile within the anticipated total number of 40 patients.

5.3.2.1.1 Dose Optimization Cohorts (Cohorts 1a and 1b) Schema

The dose optimization cohort schemas for the 3 + 3 and step-up doses are shown in Figure 2.

Figure 2: Dose Optimization Cohorts Schema: 3 + 3 and Step-up Dosing



The dose optimization cohort decision guide for the 3 + 3 dose design is shown in Table 7.

Table 7: Dose Optimization Cohort Decision Guide for the 3 + 3 Dose Design

Number of Patients with DLT at a Given Dose Level	Dose Optimization Cohort Decision Guide (3 + 3 Dose Design)
0 out of 3	Enter 3 patients at the next higher dose level (see Figure 2).
1 out of 3	If only 1 of 3 patients experiences a DLT, then 3 additional patients will be entered at the same dose level. If 1 of 6 patients experiences a DLT, the dose will be increased to the next higher dose (see Figure 2).
≥ 2	If 2 or more patients within a cohort experience DLTs, dose escalation will stop and the 3 + 3 dose optimization schema is complete (see Figure 2). Three new patients will be enrolled in the step-up dose optimization schema starting at the previously tolerated dose established in the 3 + 3 dose optimization schema as determined by the SRC; patients will individually step-up dosing by increments of 0.002 mg/kg at each cycle.

Abbreviations: DLT = dose-limiting toxicity; SRC = Safety Review Committee.

In the dose optimization step-up cohort, individual patients are allowed to step-up their dose at increments of 0.002 mg/kg. The dose optimization cohort decision guide for the step-up cohort (Cohort 1b) dose design is shown in Table 8. The decision to proceed to Cohort 1b will be the Sponsor's and based on safety and tolerability data from Cohort 1a.

Table 8: Dose Optimization Cohort Decision Guide for the Step-up Dose Design

Number of Patients with DLT at a Given Dose Level	Dose Optimization Cohort Decision Guide (Step-up Dose Design)
0	If 0 patients experience a DLT, patients continue to step-up their individual dose by increments of 0.002 mg/kg up to 0.012 mg/kg or patients can remain at their maximum tolerated step-up dose. Alternatively, the SRC may decide to enroll 3 new patients at the previously tolerated dose and step up dosing by increments of 0.002 mg/kg at each cycle.
1	If only 1 patient experiences a DLT, enroll 3 additional patients at the same dose schedule. Alternatively, the SRC may decide to enroll 3 new patients at 0.006 mg/kg and step up the individual patient dose by increments of 0.002 mg/kg at each cycle.
≥ 2	If 2 or more patients experience DLTs at a given dose level, dose escalation will be stopped; the MTD will be established in that cohort.

Abbreviations: DLT = dose-limiting toxicity. MTD = maximum tolerated dose; SRC = Safety Review Committee.

The dose-limiting toxicity (DLT) evaluation period for the 3 + 3 and step-up dose optimization cohorts will be 3 weeks (21 days) (Table 9). Any DLT past the DLT window is a delayed DLT.

Table 9: Treatment Cycle Duration and DLT Window (3 + 3 and Step-up Cohorts)

Dosing Schedule of NKTR-214	Cycle Definition	DLT Window
3 + 3 dosing q3w	21 days	21 days from Cycle 1
Step-up dosing q3w	21 days	21 days post administration, Cycle 1 of highest NKTR-214 step-up dose

Abbreviations: DLT = dose-limiting toxicity; q3w = every 3 weeks.

For the 3 + 3 dose optimization schema, patients will be enrolled in groups of at least 3 patients starting at a dose of NKTR-214 0.008 mg/kg 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 5.11.1. For the 3 + 3 dose optimization cohort (Cohort 1a), 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. 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 in 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, dose escalation will stop and the 3 + 3 dose optimization schema is complete (see Figure 2). Three new patients may be enrolled in the step-up dose optimization schema, starting at the previously tolerated dose as established in the 3 + 3 dose optimization schema as determined by the SRC; patients will individually step-up dosing by increments of 0.002 mg/kg at each cycle.

For the step-up dose optimization cohort (Cohort 1b), if a patient does not experience a DLT during the DLT evaluable period, he or she can continue to step-up their individual dose by increments of 0.002 mg/kg up to 0.012 mg/kg or a patient can remain at 1 dose level below his or her maximum tolerated step-up dose if a DLT is experienced. If only 1 patient experiences a DLT, 3 additional patients are enrolled at the same dose schedule. Alternatively, the SRC may decide to enroll 3 new patients at 0.006mg/kg and step up the individual patient dose by increments of 0.002 mg/kg at each cycle. If 2 or more patients experience DLTs, step-up dose escalation will be stopped and the MTD and an optimal dosing schedule will be established in this cohort.

At the Investigator's discretion, step-up dose increases may be delayed by 1 cycle. Moreover, the SRC or Sponsor may determine that inadequate information has been obtained in a cohort of

3 patients and may enroll additional patients to further assess the benefit/risk profile at a given dose level.

All drug-related AEs after the DLT window will continue to be collected and evaluated by the Sponsor on an ongoing basis and may be taken into consideration in determining the MTD and further dose escalation. 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.

5.3.2.2 Dose Expansion Cohorts 2 and 3

Patients in the dose expansion cohorts will start at a dose of 0.006 mg/kg. Based on review of efficacy and safety data from Cohort 2, Cohort 3 may be opened for enrollment with dosing starting at 0.010 mg/kg. Following data review for safety and efficacy, additional patients in these cohorts may be dosed using the findings from the dose optimization cohorts.

5.3.2.3 Dose Expansion Cohorts 4 and 5

Based on review of efficacy and safety data from Cohort 2 (and Cohort 3 if available), then Cohorts 4 and 5 may begin enrollment. Dosing will start at one of the doses identified in Cohort 2 or Cohort 3.

Safety Run-in (Cohorts 4 and 5 Only)

The treatment combinations planned for Cohorts 4 and 5 have not previously been evaluated in the planned patient populations. These cohorts will be dosed using a rolling 6-patient design to evaluate for toxicity and safety.

Cohorts 4 and 5 will begin in parallel, and each cohort will undergo a run-in period, in which 6 patients are planned to be enrolled to initially inform the safety profile and determine the RP2D; more or fewer patients may be enrolled depending on how many patients are response-evaluable based on the totality of the safety data for these initial patients.. A Safety Review Committee (SRC) will evaluate the safety, tolerability, and available PK of the treatment combination used in each of the 2 cohorts and may confirm the RP2D or recommend dose modification based on the first 6 evaluable patients who have completed the first treatment cycle or had a DLT during the first treatment cycle for each treatment arm. Patients participating in the safety-run in period who are not evaluable for DLTs may be replaced.

If Cohorts 4 and 5 meet the safety evaluation criteria, each of these cohorts may be expanded to approximately 63 response-evaluable patients.

5.3.3 Rationale for Dose of NKTR-214

Based on the findings from the NKTR-214 monotherapy study (EXCEL; 15-214-01) (see Section 2.1.4.1) and findings from the dose-escalation part of the PIVOT-02 study (16-214-02) (see Section 2.1.4.2), the RP2D of NKTR-214 in combination with nivolumab 360 mg q3w was

determined to be 0.006 mg/kg in the PIVOT-02 study (16-214-02), as described in more detail below.

Two data analyses of patients receiving NKTR-214 and nivolumab in Study 16-214-02 are provided; first, the rationale for the RP2D of NKTR-214 0.006 mg/kg in combination with nivolumab 360 mg q3w based on a data cut of 05 October 2017, and second, safety and efficacy data.

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 10 and see Clinical Experience with NKTR-214 in Section 2.1.4). In the dose escalation phase of PIVOT- 02 (16-214-02), the safety of NKTR-214 in combination with nivolumab at doses shown in Table 10 was assessed in 38 patients.

Additional rationale for dosing in Cohorts 3, 4, and 5 is provided in Section 2.1.7.

Table 10: Patient Exposure Supporting the RP2D of NKTR-214 0.006 mg/kg in Combination with Nivolumab 360 mg q3w

Study	NKTR-214 Dosing Frequency	Nivolumab (Flat Dose[a]) Dosing Frequency	NKTR-214 Dose (mg/kg)	No. Patients Examined for Safety	Positive [redacted] Data and/or Evidence of Clinical Activity?
NKTR-214 Monotherapy (EXCEL; 15-214-01)	q3w	n/a	0.003, 0.006, 0.009, 0.012	22	Yes
	q2w	n/a	0.006	6	Yes
NKTR-214 + Nivolumab (PIVOT-02; 16-214-02)	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; RP2D = recommended Phase 2 dose.

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 05 October 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 the RP2D of NKTR-214 0.006 mg/kg in combination with nivolumab 360 mg q3w.
- 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 05 October 2017 for 34 patients, including 10 with metastatic melanoma, 19 with RCC, and 5 with NSCLC. Of the 34 response-evaluable patients, 24 were treated at 0.006 mg/kg NKTR-214 with nivolumab 360 mg flat dose q3w; 17 patients had partial or complete responses and 13 had stable disease. Given the totality of data, including safety/tolerability, reproducible PK, dose-independent PD profile, immune cell activation, and promising efficacy data (see Clinical Experience with NKTR-214 in Section 2.1.4), the Safety Review Committee approved NKTR-214 0.006 mg/kg q3w plus nivolumab 360 mg q3w as the recommended dose to be administered in the expansion cohorts included in Part 2 of Study 16-214-02.

5.3.3.1 Update of Safety and Efficacy Data

As of 28 October 2019, 541 patients have been dosed in Study 16-214-02: 488 patients on the "doublet treatment" of NKTR-214 plus nivolumab (64 patients are still on study treatment), 43 patients on "triplet" treatment with NKTR-214 plus nivolumab plus ipilimumab (18 patients still on study), and 10 patients with NKTR-214 and nivolumab plus other anti-cancer study drugs excluding ipilimumab (5 patients still on study treatment).

The most frequently reported TEAEs were fatigue (54.3%), pyrexia (50.6%), nausea (42.0%) pruritus (39.7%), decreased appetite (37.5%), diarrhoea (31.1%) and influenza-like illness (31.1%). The most frequently reported treatment-related TEAEs were fatigue (49.4%), pyrexia (45.3%), pruritus (37.0%), nausea (32.9%) and influenza-like illness (30.5%). Grade ≥ 3 adverse reactions most frequently reported in combination Study 16-214-02 were the following grouped terms: syncope in 18 patients (3.3%): 15 patients (3.1%) in the NKTR-214 plus nivolumab

doublet cohort and 3 patients (7.0%) in the NKTR-214 plus nivolumab plus ipilimumab triplet cohort; hypotension in 17 patients (3.1%): 13 (2.7%) in the doublet cohort, 2 (20%) in the doublet plus chemotherapy cohort, and 2 patients (4.7%) in the triplet cohort; fatigue in 15 patients (2.8%): 12 (2.5) in the doublet cohort and 3 (7.0%) triplet; and rash in 12 (2.2%): 10 (2.0%) in the doublet cohort and 2 (4.7%) in the triplet cohort. The most frequently reported serious adverse reactions were flu-like symptoms in 16 patients (3.0%): 15 (3.1%) in the doublet cohort, and 1 (2.3%) in the triplet cohort; and hypotension in 12 patients (2.2%), 10 (2.0%) in the doublet cohort, and 2 (20%) in the doublet cohort plus other anti-cancer study drug patients.

See Section 2.1.4.2 for detail of AEs and SAEs by regimen in the expansion phase.

As of the 29 October 2018 cutoff date, 37 patients (including 11 with metastatic melanoma, 21 with RCC, and 5 with NSCLC) in the dose escalation phase of Study 16-214-02 had tumor response data (per RECIST 1.1) and were considered evaluable for efficacy. Of the 37 evaluable patients, 21 patients (56.8%) achieved a response (ORR) by RECIST 1.1; 4 patients (10.8%) had complete responses (Table 11). See Section 2.1.4.2 for additional data on current response rates and PD-1/PD-L1 status.

Table 11: Overall Tumor Response by Cancer Type: PIVOT-02 Combination Therapy Study 16-214-02 (Dose Escalation Phase)

	Melanoma (1L) (N = 11)	RCC (1L) (N = 14)	RCC (2L) (N = 7)	NSCLC (N = 5)	Total (N = 37)
ORR (CR + PR)	7 (63.6%)	10 (71.4%)	1 (14.3%)	3 (60.0%)	21 (56.8%)
CR	2 (18.2%)	1 (7.1%)	0	1 (20.0%)	4 (10.8%)
PR	5 (45.5%)	9 (64.3%)	1 (14.3%)	2 (40.0%)	17 (45.9%)
SD	3 (27.3%)	1 (7.1%)	6 (85.7%)	1 (20.0%)	11 (29.7%)
DCR (CR + PR + SD)	10 (90.9%)	11 (78.6%)	7 (100.0%)	4 (80.0%)	32 (86.5%)
PD	1 (9.1%)	3 (21.4%	0	1 (20.0%)	5 (13.5%)
Duration of Response (Month)	n = 7	n = 10	n = 1	n = 3	n = 21
Median	NA	NA	NA	NA	NA
Range[a]	4.5+, 12.0+	1.0+, 8.2+	10.0+, 10.0+	5.5+, 6.5+	1.0+, 12.0+
Time to Response (Month)	n = 7	n = 10	n = 1	n = 3	n = 21
Median	1.7	3.5	3.5	1.7	1.9
Range	1.4, 3.3	1.3, 7.8	3.5, 3.5	1.3, 3.7	1.3, 7.8

CR = complete response; PR = partial response; SD = stable disease; DCR = disease control rate; PD = progressive disease; ORR = objective response rate, NA = not applicable; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose.

a. The "+" indicates the response is ongoing at the time of the data cutoff.

PIVOT-02 (16-214-02) is a 2-stage design and data for either the Stage 1 (N1) population alone or in combination with Stage 2 (N2; expansion) populations were presented depending on data maturity. Data was presented only in the response-evaluable population (defined as having received 1 dose of study treatment and having undergone at least 1 scheduled postbaseline scan). The 1L melanoma and 1L RCC indications include dose escalation and expansion patients, however, the 1L urothelial indication includes expansion patients only.

As of the 29 May 2018 cutoff, in the dose expansion phase, 26 1L RCC patients and 10 1L urothelial cancer response-evaluable patients met the prespecified efficacy parameters. Twelve of 26 efficacy patients (46%) achieved a response (ORR). Responses were seen in both PD-L1 (+) (2 of 7 patients, 29%) and PD-L1 (–) (9 of 17 patients, 53%). Six of 10 urothelial 1L efficacy patients (60%) achieved a response (ORR). Responses were seen in both PD-L1 (+) (3 of 5 patients, 60%) and PD-L1 (–) patients (3 of 5 urothelial patients, 60%).

As of the 11 October 2018 cutoff, 38 1L melanoma patients met prespecified efficacy parameters; 20 of 38 1L melanoma patients achieved a response (ORR). Nine of 38 patients (24%) had a complete response. Responses were seen in both the PD-L1 (+) (defined as PD-L1 expression ≥ 1% on tumor cells) and PD-L1 (–) (defined as < 1% PD-L1 expression on tumor cells) populations with an ORR 13 of 19 patients (68%) in the PD-L1 (+) population and 6 of 14 patients (43%) in the PD-L1 (–) population (Table 12).

Table 12: Overall Tumor Response by Cancer Type: PIVOT-02 Combination Therapy Study 16-214-02 - Patients who met Pre-specified Efficacy Parameters

	Melanoma (1L) RP2D[a] (N = 38)	RCC (1L) RP2D[a] (N = 26)	Urothelial (IL)[a] (N = 10)
Best Overall Response			
ORR (CR + PR)	20 (53.0%)	12 (46.0 %)	6 (60.0%)
CR	9 (24%)	NA	NA
PD-L1 Negative[b]	n = 14	n = 17	n = 5
ORR (CR + PR)	6 (43.0%)	9 (53.0%)	3 (60.0%)
PD-L1 Positive[c]	n = 19	n = 7	n = 5
ORR (CR + PR)	13 (68.0%)	2 (29.0%)	3 (60.0%)
PD-L1 Unknown	n = 5	n = 2	n = 0
ORR (CR + PR)	1 (20.0%)	1 (50.0%)	0
Disease Control Rate			
DCR (CR + PR + SD[d])	29 (76.0%)	20 (77.0%)	7 (70.0%)
Time on Study (Month)	**n = 41[e]**	**n = 26**	**n = 10**
Median	5.8	5.6	3.9

CR = complete response; DCR = disease control rate; IHC = immunohistochemistry; NA = not available; ORR = objective response rate, PD = progressive disease; PD-L1 = programmed cell death ligand 1; PR = partial response; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose ; SD = stable disease; TEAE = treatment-emergent adverse event

a. Melanoma 1L and RCC 1L include both escalation and expansion patients. Urothelial includes expansion patients only.

b. PD-L1 negative tumors with < 1% of staining on tumor cell via IHC.

c. PD-L1 positive tumor with ≥ 1% of staining on tumor cell via IHC.

d. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study (RECIST 1.1).

e. Includes 3 patients who were not considered response-evaluable in the Stage 1 (N1) and Stage 2 (N2) populations (all 3 patients discontinued prior to first scan due to an unrelated TEAE [n = 1] and Patient Decision [n = 2]).

Source: Diab 2018b and Diab 2018a.

5.3.3.2 Rationale for NKTR-214 Doses in the Dose Optimization Cohorts

While the RP2D of NKTR-214 in combination with nivolumab is 0.006 mg/kg, the MTD in combination with pembrolizumab has yet to be determined. In the 15-214-01 study, only 1 patient who had a BMI > 30 received a monotherapy dose of NKTR-214 at 0.012 mg/kg. This

patient experienced DLTs of syncope and hypotension (a known adverse event (AE) associated with both IL-2 and engineered cytokines). These AEs resolved within 3 days.

Hypotension is identified as an important risk in NKTR 214 monotherapy Study 15-214-01 as well as in other ongoing combination studies. To mitigate this risk, hypotension management guidelines were successfully implemented (See Section 2.1.4.1). Safety data with NKTR-214 0.006 mg/kg in combination with nivolumab 360 mg q3w in the PIVOT-02 study (16-214-02) showed a lower incidence of treatment-related hypotension (59 of 358 patients, [16.5%]) with the implementation of hypotension management guidelines. The successful management of hypotension using the hypotension guidelines supports further exploration with higher doses of NKTR-214 than 0.006 mg/kg.

Starting with Amendment 5.0 and subsequent amendments, to further investigate the MTD of NKTR-214 in combination with pembrolizumab in patients with locally advanced or metastatic solid tumors, NKTR-214 will be administered at a starting dose of 0.008 mg/kg in the 3 + 3 dose optimization schema and at the previously tolerated dose established in the 3 + 3 dose optimization schema as determined by the SRC in the step-up dose optimization schema. Details of the dose optimization schema are provided in Section 5.3.2.1.

5.3.4 Monitoring, Vital Signs, Hydration Guidelines, and Premedication for Flu-like Symptoms.

The study site must be equipped for medical emergencies.

5.3.4.1 Frequent Vital Signs

Vital signs (Section 7.16) are to be taken and recorded prior to NKTR-214 dosing and monitored and recorded following the completion time of the pembrolizumab administration. For Cycle 1 only, monitoring windows will be as follows:

During all cycles and beyond on dosing days monitor and record vital signs predose (NKTR-214) and approximately 1 hour after administration of pembrolizumab on Day 1.

- Cycle 1 Day 3: monitor one time at 48 hr ± 3 hr from start of infusion of NKTR-214
- Cycle 1 Day 8: monitor one time at 168 hr ± 24 hr from start of infusion of NKTR-214
- EOT: monitor one time at 90 (± 10 days)

If the patient experienced a Grade ≥ 2 infusion-related reaction or hypotension on the dosing day, the patient may be monitored overnight or for a longer period at the discretion of the Investigator.

5.3.4.2 Hydration Guidelines

Important safety information and hydration instructions are to be provided to patients. Details regarding intravenous and oral hydration will be captured in the EDC.

Adequate hydration mitigates the development of hypotension associated with NKTR-214 administration. Hydration and renal function must be assessed within 72 hours, or as soon as locally feasible, prior to NKTR-214 study drug administration see Appendix 1 for the list of analytes that require collection and evaluation prior to NKTR-214 study drug administration). For participants who must delay study treatment due to creatinine increase, see additional information regarding criteria to delay (Sections 5.13.1 and 5.13.2), resume (Section 5.13.6), or permanently discontinue study treatment (Section 5.15). Underlying reasons for decreased oral intake (eg, nausea) should be addressed and treatment (eg, IV hydration) should be provided. The Investigator may modify these recommendations based on the needs of the individual patient.

Patients should be administered 1 liter of IV fluid on the day of each dosing of NKTR-214. In addition, consider administering 1 liter of normal saline IV when the patients return for clinic visits (eg, if the patient returns for PK draws on Days 3 and 5 of Cycle 1), anytime based on the patient's need, or as clinically indicated. Patients are to be instructed that for the next 3 days after administration of NKTR-214, they should 1) drink at least 2 liters per day of self-administered oral hydration and 2), keep bedside drinking water at night and avoid posture change from sitting to standing without hand support and activity which may contribute to dehydration (including, but not limited to, strenuous activity, long hot showers, sunbathing, and saunas) for at least 3 days following treatment with NKTR-214.

Antihypertensive medications (including diuretics) should be withheld from Day 1 to Day 5 of each Cycle. Antihypertensive medications may be restarted on Day 6 or at any time as clinically indicated (eg, based on blood pressure measurements).

Per clinical judgment, IV fluids may be administered at any time during any cycle. The Investigator may decide to forego administering IV fluids to a patient or adjust the recommendation for self-oral hydration to a particular patient if this is deemed in the best interest of the patient (eg, evidence of fluid overload). Advise patients 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. Co-management with an endocrinologist is recommended for patients with pre-existing adrenal insufficiency.

Between 2 and 4 days (inclusive) following treatment with NKTR-214, 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.

5.3.4.3 Premedication for Flu-like Symptoms

These recommendations have been developed to reduce the risk of flu-like symptoms during the first week of each treatment cycle. Investigator may modify these recommendations based on the needs of individual patient.

- Administer acetaminophen (eg, 650 mg every 6 hours) or NSAIDs (eg, ibuprofen 400 mg every 6 hours) a minimum of 30 minutes prior to treatment on Day 1 of each cycle.
- Administer acetaminophen or NSAIDs q6h on Day 2 to 5 of each cycle. For Cohort 4, premedication can only be done with acetaminophen.
- Instruct patients on the signs and symptoms (fever over 100.4 °F or 38 °C, chills and sweats, muscle aches or join paint, fatigue and weakness), how to treat with acetaminophen or NSAIDs, and when to call their treating oncologist or present for medical care.

5.3.5 Duration of Treatment

Patients will be treated until:

- A maximum of 2 years (or a maximum of 34 cycles) of treatment have been completed
- Disease progression
- Death
- Unacceptable toxicity
- Symptomatic deterioration
- 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

5.3.6 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 (Wolchok 2009, Nishino 2015).

Criteria: Patients are permitted to continue study treatment beyond initial PD per RECIST 1.1 as assessed by the Investigator if they meet the following criteria:

- Investigator-assessed clinical benefit.

- All eligibility criteria, including ECOG performance status of 0 or 1
- Absence of signs and symptoms indicating clinical disease progression (eg, increased pain or worsening laboratory values)
- Absence of tumor progression at critical anatomical sites (eg, brain metastases or cord compression) requiring urgent intervention.
- Provides written informed consent for treatment beyond progression.
- Approval of Medical Monitor

Assessments. Radiographic scans and other assessments should continue in accordance with the Schedule of Events (Section 1.1) for the duration of the treatment beyond progression.

Discontinuation. Treatment beyond progression should be stopped when the Investigator assesses a loss of clinical benefit. The criteria may include clinical disease progression, second PD of target lesions per RECIST 1.1, radiographic progression of non-target lesions, or new lesions or high grade, unresolved treatment related toxicity. Discussion with the medical monitor is encouraged

5.4 End of Treatment (EOT)

Patients may choose to discontinue the trial at any time and for any reason. Patients may discontinue treatment of all or one of the study drugs based on AEs. Reasons for permanent treatment discontinuation are detailed in Section 5.15. The EOT visit should occur 30 (± 10) days after all study therapy is permanently discontinued or before a new antineoplastic regimen (including commercially-sourced single-agent pembrolizumab) starts. If the patient discontinues NKTR-214 but continues on pembrolizumab and/or chemotherapy, the NKTR-214 immunogenicity EOT sample should be collected at 30 ((± 10) days after the last dose of NKTR-214.

If a patient withdraws consent, 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 1.1).

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

5.5 Long-term Follow-up

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

- Upon discontinuation of all study treatment, the long-term follow-up visits should occur every 90 (± 10) days after the last dose of all study treatment and then every 90 (± 10) days for survival status. Per clinical judgment, the patient may come in earlier.

- If a patient did not experience PD per BICR by RECIST 1.1 when study drug treatment was discontinued, tumor assessments should continue every 90 (± 10) days until PD, consent withdrawal, start of new antineoplastic regime, death, or study termination by Sponsor.
- A sample for immunogenicity testing for NKTR-214 will be collected at the first 90-day follow up visit.

For AE and serious AE (SAE) reporting periods, please refer to Sections 7.5 and 7.6.

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 must be performed at Screening, every 9 weeks (± 7 days) from Cycle 1 Day 1, EOT, and at the 90-day long-term follow-up visits. If a patient has an unconfirmed PR or CR, an early scan is recommended 4 weeks or later, and the next scheduled 9-week scan may be skipped if less than 4 weeks from the early scan. All subsequent tumor assessments must remain on the original 9-week assessment schedule based off Cycle 1 Day 1 (ie, at Weeks 18, 27, 36, etc.). Patients with unconfirmed stable disease / progressive disease, subsequent tumor assessments must remain on the original 9-week assessment schedule unless an early scan is clinically indicated. Assessments will become less frequent during the long-term follow-up period (Section 5.5). Tumor response will be evaluated using RECIST 1.1 (Section 8.0). If a patient does not experience PD by RECIST 1.1 when study drug treatment was discontinued, tumor assessments should continue every 90 (± 10) days until PD, consent withdrawal, start of new systemic therapy, death, or study termination by Sponsor. Confirmation of tumor response is discussed in Section 8.2.2.3.

A brain MRI at Screening is required for all patients with metastatic NSCLC, and for patients with other tumor types who have known brain metastasis. Subsequent brain MRIs for all cohorts may be done at 9-week intervals if clinically indicated.

Documented tumor assessments are required using CT scans, MRI, and/or physical examination, as appropriate. Radiographic assessments (chest/abdomen/pelvis) are required for all patients for tumor assessments. CT with intravenous contrast (at 5 mm thinness or less) is the preferred method. For patients with contrast allergies, chest CT without contrast and abdomen/pelvis MRI with gadolinium are alternatives. A CT portion of the PET-CT is acceptable if RECIST 1.1 measurements can be performed. Note that for Germany only, pelvic radiographic assessment is not applicable.

The same method of assessment (CT or MRI) and the same technique for acquisition of images must be used for all study assessments (contrast must be used unless medically contraindicated).

Baseline imaging must 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.

5.8 Pharmacokinetic Measurements

Blood samples for PK analyses of NKTR-214 and its metabolites will be collected as described below.

Dose Optimization 3 + 3 Cohort (Cohort 1a): for Cycle 1 only, blood will be collected at predose on Day 1 and at the following times after the start of the NKTR-214 infusion: 3 hr ± 30 min (Day 1), 48 hr ± 3 hr (Day 3), 96 hr ± 24 hr (Day 5), and 168 hr ± 24 hr (Day 8).

For Cycle 2 and every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc.), blood will be collected on predose on Day 1. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing.

Dose Optimization Step-up Cohort (Cohort 1b): for Cycle 1 and only in the first cycle of any subsequent cycle(s) in which the patient is administered a step-up dose, the PK sampling schedule is the same as shown above for Cycle 1 for Cohort 1a.

With the exception of cycles in which the patient is administered a step-up dose, for Cycles 2 and every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc.), blood will be collected on predose on Day 1. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing.

Dose Expansion Cohorts (Cohorts 2, 3, 4, and 5): for Cycle 1, blood will be collected predose on Day 1 and at the following times after the start of the NKTR-214 infusion: 3 hr ± 30 min (Day 1), 48 hr ± 3 hr (Day 3), 96 hr ± 24 hr (Day 5), and 168 hr ± 24 hr (Day 8).

For Cycle 2 and every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc.), blood will be collected predose on Day 1. For Cycles 2 and beyond, predose sampling assessments can be drawn within 72 hours prior to dosing.

If a possible study drug(s)-related SAE occurs on study, PK blood samples should be drawn as close to the event as possible to help characterize any possible relationships between drug exposure and the SAE.

Blood samples for PK analysis will be collected and processed according to the Laboratory Manual provided to the site. All PK sample collections should align with days of study drug administration and adjusted for any dose delays. 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 at predose on Day 1 of Cycle 1, and Cycle 2, and predose on Day 1 of every 3 cycles after Cycle 2 (ie, Cycles 5, 8, 11, etc.), at the NKTR-214 EOT visit, and at 90 (± 10) days after the last administered dose of NKTR-214. If dosing occurs on a different day, the immunogenicity sampling should be adjusted accordingly.

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

5.10.2 Tumor Tissue Biopsy Collection Times and Analysis

All patients must provide tumor tissue from resection or biopsy obtained within 12 months from screening as either formalin-fixed paraffin-embedded (FFPE) block or unstained slides (a minimum of 10 slides freshly-cut within 1 week of submission) (Table 13). Tissue obtained from fine needle aspiration, cytology specimen and bone lesion are NOT acceptable. A tracking number confirming shipment of the sample to the central lab must be supplied before Cycle 1 Day 1. Unused portions of the block will be returned to the site. If archival tissue is not available, or if patient received systemic anticancer therapy between dates of tissue collection and screening, a fresh biopsy is required.

Target lesions should not be biopsied.

One on-treatment tumor biopsy (submitted as a block if possible) will be collected during Days 15-21 in Cycle 1 for the dose optimization cohorts only. No Day 15 to 21 on-treatment tumor biopsies will be collected for the dose expansion cohorts. If screening biopsies (fresh or archival) are not obtained, on-treatment biopsies should not be collected.

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.

Table 13: Tumor Biopsy Requirements (Dose Optimization and Dose Expansion)

Requirements[a]		
Visit	**Recommendation**	**Specimen Type**
Screening	All Patients[b]	Fresh biopsy or archival biopsy (block preferred, but slides [minimum of 10] acceptable)
Week 3 (Days 15-21)	Dose Optimization only	Fresh biopsy

a. Fine needle aspiration, cytology specimens, and bone lesions are not acceptable. Target lesions should not be biopsied unless there are no other lesions suitable for biopsy. Pretreatment and on-treatment biopsies should be taken from the same lesion, if feasible.
b. Acceptable tissue specimens include archival tissue (10 slides) obtained no more than 12 months prior to enrollment if the patient has not received systemic treatment between the time of biopsy/resection and enrollment. Otherwise, a fresh tumor biopsy taken during screening is required.

5.11 Determination of Dose Limiting Toxicities (DLTs)

Based on the nonclinical toxicology, safety data from the dose escalation study (Study 15-214-01) and PIVOT-02 (16-214-02) and the peak pharmacokinetic and pharmacodynamic profile of NKTR-214, drug-related toxicity is most likely to occur 1 to 5 days following treatment. Dose limiting toxicities will be assessed during the DLT window shown in Table 9. If DLTs are not observed, dose escalation will be permitted. Patients will continue to enroll until 40 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 (encephalopathies, myasthenic syndromes, Guillain-Barre syndrome).
- Any Grade 4 drug-related hematological AE that is clinically significant (neutropenia, leukopenia, thrombopenia) > 7 days and any Grade 4 anemia.
- Any Grade 4 drug-related nausea or vomiting.

- Any Grade ≥ 3 drug-related hypotension lasting > 48 hours postdose, cytokine-release syndrome, capillary leak syndrome, pulmonary edema, or symptomatic hypereosinophilic syndrome.
- Any case of Hy's law (https://www.fda.gov/downloads/Guidances/UCM174090.pdf).

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 postdose.
- Fatigue that improves to ≤ Grade 2 within 7 days.
- Amylase or lipase elevations that last ≤ 7 days and are not associated with symptoms or clinical manifestation of pancreatitis.

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 9. 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 one drug are allowed for management of treatment-related toxicities during a given treatment cycle for all cohorts. Any dose delays or reduction in all cohorts will require discussion and approval of the medical monitor. 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 Pembrolizumab and Chemotherapy Dose Delay and Reduction Criteria

5.13.1.1 Pembrolizumab (All Cohorts)

Dose reductions for pembrolizumab are not permitted in this study. Pembrolizumab may be delayed based on drug-related toxicities and the medical monitor should be informed by the Investigator of any pembrolizumab dose delay. Refer to the Keytruda (pembrolizumab) full prescribing information for the conditions that warrant a delay in dosing. NKTR-214 administration can continue independent of the pembrolizumab dose delay.

5.13.1.2 Chemotherapy (Cohorts 4 and 5 Only)

For Cohorts 4 and 5: Reduction of 1 chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the Investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of three agents, all three agents should be reduced (if applicable), interrupted or discontinued according to the recommended dose modifications.

Patients may continue on single study treatment drug if other study drug is discontinued for protocol defined reasons or at investigator's medical judgement, example patient may continue receiving NKTR-214 if discontinued from pembrolizumab and/or chemotherapy. Subjects may also have chemotherapy discontinued and continue on pembrolizumab alone. Similarly, subjects may discontinue pembrolizumab and continue on chemotherapy alone during the first four cycles, if appropriate.

Chemotherapy may be interrupted for a maximum of 6 weeks; pembrolizumab may be

interrupted for a maximum of 12 weeks. Refer to approved product labels for dose modifications regarding paclitaxel and nab-paclitaxel.

Pemetrexed, carboplatin, and cisplatin dose delay, reduction, and discontinuation criteria are shown below in Table 14.

Table 14: Pemetrexed, Carboplatin, and Cisplatin Dose Delay, Reduction, and Discontinuation Criteria

Discontinuation Criteria:				
	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
Recommended Dose Modifications for Chemotherapy Non-hematological Toxicity:				
		Pemetrexed	**Cisplatin**	**Carboplatin**
Event	**CTC Grade**	**Dose level (DL)**		
Nausea or vomiting	Grade 3 or 4	DL 0	DL 0	DL 0
Diarrhea	Grade 3 or 4	DL -1	DL -1	DL 0
Mucositis	Grade 3 or 4	DL -2	DL 0	DL 0
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3 or 4	DL -1	Discontinue	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3 or 4	DL -1	DL -1	DL -1
Recommended Dose Modifications for Chemotherapy Hematological Toxicity:				
			Pemetrexed	**Cisplatin/Carboplatin**
Platelets	**ANC**		**Dose level (DL)**	
≥ 50 AND	≥ 0.5		DL 0	DL 0
≥ 50 AND	< 0.5		DL -1	DL -1
< 50 without bleeding AND	ANY		DL -1	DL -1
< 50 with Grade ≥ 2 bleeding AND	ANY		DL -2	DL -2
ANY AND	< 1.0 + fever ≥ 38.5°C (101°F)		DL -1	DL -1

Creatinine clearance (CLcr) will be calculated by the Cockcroft-Gault equation (Cockcroft 1976). CLcr must be ≥ 45 mL/min prior to the administration of chemotherapy. Pemetrexed 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 CLcr value has not returned to ≥ 45 mL/min within 42 days after the previous dose, platinum and/or pemetrexed must be discontinued.

5.13.2 NKTR-214 Dose Delay and Reduction Criteria

With approval of the Sponsor's Medical Monitor, the NKTR-214 dose may be delayed or reduced due to toxicities. Pembrolizumab administration can continue independent of the NKTR-214 dose reduction or delay.

NKTR-214 administration should be delayed for the following reasons:

- For persistent Grade 2 related toxicity, at the discretion of the Investigator.
- Grade ≥ 2 creatinine increase:
  - Treatment should be delayed. Participant may resume study drug when serum creatinine has returned to Grade ≤ 1, as assessed within 24 hours prior to redosing.
- 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 5.15), with the following exceptions:
  - Grade ≥ 3 lymphopenia
  - Grade ≥ 3 asymptomatic amylase or lipase elevation
- Patient has acute infection (eg, 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 5.13.6).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

NKTR-214 dosing may resume at the same or reduced NKTR-214 dose level depending on the toxicity resolution to Grade 1 or a return to baseline with adequate symptom management, except for instances where the potential recurrence of the event poses an undue risk for the participant. Medical Monitor consultation is required for dose reduction.

5.13.3 Dose-Modification Criteria for NKTR-214 for Cycle 1 ALT/AST Elevations

These recommendations are for Cycle 1 only and are not intended to serve as rigid guidelines or to replace clinical judgement. Subsequent cycles should follow standard Hepatic Adverse Event Management Algorithm (Pharmacy Manual).

Rule out non-inflammatory etiologies. If non-inflammatory cause, treat accordingly and continue NKTR-214. Consider imaging for obstruction.

If during monitoring ALT/AST increases, follow the guidance for the highest levels.

ALT or AST > 3.0 to ≤ 5.0 × ULN (within first cycle of NKTR-214)

Increase frequency of LFT monitoring to approximately every 3 days and delay treatment until lab abnormalities resolve to Grade 0-1.

If no improvement within 7 days, treat with 0.5-1 mg/kg/day prednisone equivalents, and taper steroids over at least 1 month before resuming treatment

ALT or AST > 5.0 to ≤ 8.0 × ULN (within first cycle of NKTR-214)

Increase frequency of monitoring to approximately every 3 days until lab abnormalities resolve to Grade 0-1.

Treatment must be delayed until lab abnormalities resolve to Grade 0 to 1.

If no improvement within 7 days (follow Hepatic Adverse Event Management Algorithm);

- Discontinue NKTR-214
- 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least 1 month
- Consult gastroenterologist
- Consider adding non-corticosteroid immunosuppressive medication if no improvement in > 3-5 days, worsens or rebounds while on steroids

ALT or AST > 8.0 × ULN (follow Hepatic Adverse Event Management Algorithm)

- Discontinue NKTR-214
- Increase frequency of monitoring to approximately 1 to 2 days
- 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least 1 month
- Consult gastroenterologist
- If no improvement in > 3 to 5 days, worsens or rebounds, add non-corticosteroid immunosuppressive medication

Please refer to Section 5.15 for discontinuation criteria.

5.13.4 Monitoring and Management of Elevated Hepatic Transaminases

Elevated hepatic transaminases are an overlapping toxicity that can occur for NKTR-214. 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 laboratory abnormalities with these characteristics have been observed in PIVOT-02 during Cycle 1, and patients were able to continue study treatment uninterrupted with close laboratory monitoring (Section 5.13.3).

Hepatic events, including elevated liver function tests, have also been observed for pembrolizumab. 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). 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 product labeling for appropriate management.

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. Eosinophilia and eosinophilic disorders have been reported with other immunotherapy like anti-PD-1/PDL-1 inhibitors as well.

Absolute eosinophil count (AEC) should be closely monitored per protocol. If a study subject is suspected to have hypereosinophilic syndrome (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 Criteria to Resume NKTR-214

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with AST or ALT **> 3.0 to ≤ 5.0 × ULN**, and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by Medical Monitor (or designee).

- For participants who must delay study treatment due to Grade ≥ 2 creatinine increase, the patient may resume study drug treatment when serum creatinine has returned to Grade ≤ 1 creatinine increase 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 5.15).
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the medical monitor (or designee). Withhold until clinically stable or permanently discontinue depending on severity for Grade ≥ 3 adrenal insufficiency or hypophysitis. Hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should not require discontinuation.

5.14 Management Algorithms for Immune-Mediated AEs and Cytokine Release Syndrome

5.14.1 Management Algorithms for Immune-Mediated AEs Associated with Immuno-Oncology Agents

Immune mediated adverse events (IMAEs) are well defined AEs associated with the use of Pembrolizumab. The management of these AEs should be according to pembrolizumab product labeling. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed and are available as part of the pembrolizumab product labeling to assist Investigators in assessing and managing the following groups of AEs:

- Pneumonitis
- Colitis
- Hepatitis
- Endocrinopathies
- Nephritis and renal dysfunction
- Skin adverse reactions
- Neurological
- Other immune-related AEs

The term immune-related adverse events (IrAEs) is interchangeable with immune-mediated adverse events (IMAEs).

5.14.2 Management Algorithm for Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a clinical diagnosis of exclusion that usually presents with a constellation of symptoms associated with cytokine side effects such as persistent fever, hypotension, hypoxia in association with/without tachypnea, headache, rash, tachycardia, or

organ toxicity with varied manifestation. For confirmed cases of CRS or suspected CRS Grade 3 or higher, the Investigator should contact the Medical Monitor regarding treatment modifications or dose changes. A general guidance with algorithm for CRS management and reportability is provided in Appendix 4.

5.15 Discontinuation from Study Treatment

Patients MUST discontinue investigational product (and non-investigational product at the discretion of the Investigator) for any of the following reasons:

- Patient's request to stop study treatment. Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for further assessments or contact with him/her or persons previously authorized by patient to provide this information.
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the patient.
- Termination of the study by the Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, a patient who has been imprisoned may be permitted to continue as a patient. Strict conditions apply and Sponsor approval is required.)
- Disease progression in the absence of clinical benefit as determined by the Investigator (see details regarding continuing treatment beyond initial assessment of progression per RECIST 1.1 in Section 5.3.6).
- Occurrence of a clinically significant AE found to be unacceptable or nonresolution of a clinically significant AE for > 8 weeks.
- Symptomatic deterioration in the absence of tumor progression per RECIST 1.1.
- Noncompliance of the patient with protocol-mandated procedures based on the judgment and agreement of both the Investigator and Sponsor
- If a patient has not progressed following discontinuation of study drug(s), every effort should be made to continue to obtain radiographic tumor assessments (until the patient has documented progression as per the BICR).

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

Patients may choose to discontinue the study at any time, for any reason, and without prejudice to further treatment. Refer to the Schedule of Events for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

If a female patient becomes pregnant, administration of the study drug(s) must be discontinued immediately, and the Investigator must notify the Sponsor within 24 hours of awareness of the pregnancy. Refer to Section 7.12 (Pregnancy).

All patients who discontinue study treatment should comply with protocol specified follow-up procedures. The only exception to this requirement is when a patient withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the patient's completion of the study, the reason for the discontinuation must be documented in the patient's medical records and entered on the appropriate case report form (CRF) page.

Patients meeting any of the following criteria will be required to permanently discontinue all assigned study drug(s); however, with Medical Monitor approval, NKTR-214 treatment may continue if the toxicities listed below are considered related to pembrolizumab only. For CVA events and suspected TIA events, follow the criteria described below (additional details are provided in the CVA management algorithm in Appendix 2).

- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity
- Grade 3 or 4 nephritis
- AST or ALT greater than 5× ULN or total bilirubin greater than 3 × ULN
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Myasthenic syndrome/myasthenia gravis, Guillain-Barre, or meningoencephalitis (all grades)
- Grade 3 or 4 ocular inflammatory toxicity
- Grade 4 pancreatitis, or any grade of recurrent pancreatitis or Grade 4 amylase or lipase that does not return to baseline or Grade ≤ 1 within 7 days
- Grade 3 or 4 infusion-related reactions
- Grade 4 rash, severe skin reactions, or confirmed Stevens–Johnson syndrome or toxic epidermal necrolysis
- Any severe or Grade 3 treatment-related adverse reactions that recur
- 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 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 and decrease to Grade < 4 or return to baseline within 7 days
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs such as hyper- or hypothyroidism, or glucose intolerance, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids [10 mg or less of prednisone or equivalent per day], thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor
- Any 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, which 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 preferred unless contraindicated), regardless of neurological symptoms (see Appendix 2)
- For a suspected TIA event without clear alternative etiology. For a suspected TIA event without clear alternative etiology, study treatment may be continued only after careful risk-benefit assessment by the Investigator (see Appendix 2)

5.16 Treatment of NKTR-214 and Pembrolizumab, Related Infusion Reactions

Infusion reactions have been reported during infusion with NKTR-214 and pembrolizumab. If such a reaction were to occur with the NKTR-214 or pembrolizumab, it might manifest but not

limited to fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded as outlined below (consistent with CTCAE v5.0 grading of infusion related reaction; 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 [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the 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.
- 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 [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of NKTR-214 or pembrolizumab. 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. 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 (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

5.17 Prior and Concomitant Medications

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 long-term follow-up visit will be recorded, including start and stop date, dose and route of administration, frequency, and indication. Medications taken for a procedure (eg, biopsy) should also be recorded.

5.18 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. For these patients, adrenal replacement steroid doses > 10 mg daily prednisone are permitted for the first 4 days after administration of study drug(s) based on assessment of the degree of adrenal impairment and the extent of existing corticosteroid supplementation. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Prophylaxis for flu-like symptoms with either acetaminophen or NSAIDs are permitted on study per the Investigator's discretion. Prophylaxis for flu-like symptoms is initiated on Day 1 of the dosing cycle and continued through Day 5 or longer as needed. Prophylaxis with only acetaminophen is permitted for Cohort 4.

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

If a patient reports symptoms (such as nausea and/or vomiting), prophylactic use of anti-emetics may also be used.

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

1. Will be considered as having non-evaluable disease for ORR for all tumor assessments after the date of initiation of radiotherapy/surgery), and

2. 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.

5.18.1 Thromboembolism Prophylaxis and Treatment

Patients with a history of a venous or arterial thromboembolic event must be receiving or have received a stable regimen of therapeutic anticoagulation (LMWH or DOAC) as indicated by the regional clinical guidelines. Additionally:

- Use of coumadin is permitted; however, therapeutic dosing should target a specific INR stable for at least 4 weeks prior to enrollment. NKTR-214 has the potential to down-regulate metabolizing enzymes for coumadin for approximately 1 week after administration of each dose of NKTR-214. Due to the possibility of drug-drug interactions between coumadin and NKTR-214, frequent monitoring of INR and ongoing consideration of dose adjustments are warranted throughout the patient's participation on study.

5.19 Prohibited Concomitant Medications

- Immunosuppressive agents (except for such agents used as supportive care for the treatment of potential autoimmune toxicities, for example anti-IL4-alpha antibody [dupilumab] for skin toxicity, anti-integrin α4β7 antibody [vedolizumab] or anti-TNF [infliximab] for colitis symptoms).
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.18), at a daily dose ≥10 mg prednisone equivalent.

- Any antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, investigational agent or extensive non-palliative radiation therapy (except as described in Section 5.18) is prohibited during the study.
- Low-dose acetylsalicylic acid (approximately 81 mg/day) should not be combined with LMWH or DOAC due to an increased risk of hemorrhage (except as stated in Section 5.18.1).
- Herbal remedies and supplements with an approved indication for cancer are not allowed while a patient is enrolled in the study

- In addition, prohibited medications listed in the current pembrolizumab prescribing information are not allowed.

5.20 Effect of NKTR-214 on Concomitant Medication Metabolism

NKTR-214 may have the potential to affect the clearance of co-administered drugs based on its ability to modulate 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 a week after NKTR-214 administration, 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, Zídek 2009). Similar to changes that occur during a typical inflammatory response, NKTR-214 treatment may lead to downregulation 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 drug metabolizing enzymes or drug transporters. Investigators should carefully monitor patients receiving drugs with narrow therapeutic indices or drugs that are sensitive substrates of drug metabolizing enzymes or drug transporters for the occurrence of adverse effects and adjust the dose of these drugs if needed.

5.20.1 Interaction of NKTR-214 and Warfarin

For patients receiving warfarin (coumadin), therapeutic dosing should target a specific INR that is stable for at least 4 weeks prior to NKTR-214 administration. NKTR-214 has the potential to down-regulate metabolizing enzymes for warfarin for approximately 1 week after administration of each dose of NKTR-214. Due to the possibility of drug-drug interactions between warfarin and NKTR-214, frequent monitoring of INR and ongoing consideration of dose adjustments are warranted during NKTR-214 administration.

5.21 Adverse Events

After initiation of study drug treatment, all adverse events (AEs), either reported by the patient or observed by the study Investigator/staff, will be reported from the time of first study drug(s)

administration until 100 days after discontinuation of all study drug treatments or until a new antineoplastic regimen has been initiated. Exceptions to serious adverse events reporting is mentioned in Section 7.7. This trial will use the Medical Dictionary for Regulatory Activities (MedDRA) for coding all treatment emergent AEs and grading will be assessed by CTCAE version 5.0 grading criteria. AEs will be summarized by preferred term, system organ class, grade of severity, and relationship to each study drug (NKTR-214 and/or pembrolizumab).

5.22 Treatment Assignment and Patient Number Assignment

As of Amendment 5.1, Interactive Response Technology (IRT) will be employed to manage patient enrollment, cohort assignment, and drug supply for NKTR-214, pembrolizumab, and chemotherapy drugs. 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

Table 15 provides the study treatments that will be administered in the study.

Table 15: Investigational Products

Table 15: Investigational Products (Contd)

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

[redacted]

[1]

6.1 Pembrolizumab

Commercially available or locally stocked pembrolizumab will be prescribed and administered per local laws and the prescribing information.

6.2 NKTR-214 Drug Description and Formulation

[redacted]

6.3 NKTR-214 Drug Packaging and Labeling

NKTR-214 will be packaged and labeled according to current good manufacturing practices.

[redacted]

6.4 NKTR-214 Drug Reconstitution and Handling

NKTR-214 will be administered first, before pembrolizumab. NKTR-214 is to be administered as an IV infusion over 30 (± 5) minutes. Patients should be carefully monitored for infusion reactions during NKTR-214 administration.

[redacted]

Please refer to the Pharmacy Manual/current Investigator Brochure for detailed requirements regarding preparation and administration.

6.5 NKTR-214 Drug Storage

[redacted]

6.6 NKTR-214 Drug Shipment

[redacted]

6.7 Pembrolizumab, Pemetrexed, Cisplatin, Paclitaxel, Nab-paclitaxel, and Carboplatin Formulation, Reconstitution, Storage and Packaging

Please refer to the Pharmacy Manual for details.

6.8 NKTR-214 Pembrolizumab, Pemetrexed, Cisplatin, Paclitaxel, Nab-paclitaxel, and Carboplatin Drug Accountability and Reconciliation

Please refer to the Pharmacy Manual for details.

7.0 ASSESSMENT OF SAFETY

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 pre-existing conditions. Clinical laboratory, vital sign, or physical examination abnormalities will only be reported as AEs if they are deemed clinically significant by the Investigator (eg, associated with signs and symptoms, require treatment, or require follow-up). 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.

An AE does not include:

- A medical or surgical procedure (eg, 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 (eg, hospitalization for elective surgery for a condition that has not worsened on study, social and/or convenience admissions to grant families a respite in caring for a patient).
- Overdose of either study drug(s) or concomitant medication without any signs or symptoms.

7.2 Monitoring AEs

All AEs will be assessed by the Investigator and recorded, including but not limited to, the following: the event term, the date of onset and resolution, seriousness, severity, relationship to study drug(s), outcome, treatment of the event, and action taken with the study drug(s). AEs will be reported starting immediately after the patient has been administered the first dose of study drug(s) until 100 days after the last dose of all study drug(s). For treatment-related SAEs, additional reporting requirements also apply (Section 7.7).

An event occurring after the patient has provided informed consent, but before the first dose of study treatment or confirmed screen failure, 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 5.0 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 [eg, insomnia, mild headache]).
- Grade 2 = Moderate (event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment [eg, 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 pembrolizumab) as applicable will be evaluated by the Investigator using the following definitions:

- Not related: An AE that does not follow a reasonable temporal sequence from administration of study drug(s), and/or that can be reasonably explained by other factors such as the patient's pre-existing medical condition, underlying disease, concurrent illness, or concomitant medications/therapies.
- Related: There is a reasonable possibility that an AE is caused by the study drug(s). A plausible temporal sequence exists between the time of administration of the study drug(s) and the development of the AE, or it follows a known response pattern to the study drug(s). The AE cannot be reasonably explained by the known characteristics of the patient's clinical state or other concomitant therapies or interventions administered to the patient.

7.5 AE Reporting and Follow-up

After initiation of study drug treatment, all AEs except for SAEs (Sections 7.7 and 7.8) will be reported from the time of first study drug(s) administration until 90 days after the last dose of all study drug(s).

All ongoing non-serious 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.

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, ie, in the opinion of the Investigator, the places the patient at immediate risk of death from the event as it occurred; it does not include an AE 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 (eg, elective hospitalizations for social reasons or due to long travel distances or for prophylactic patient observation), 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 or confirmed screen failure, 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. All SAEs, regardless of causality attribution (ie, related or not related), with an onset within 90 days of discontinuation of all study drug treatments or until a new antineoplastic regimen has been initiated will 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.

In addition, all SAE's that occur beyond 90 days after 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 awareness of the event.

SAEs must be reported to Nektar Therapeutics Drug Safety via email or Safety Fax as listed at the beginning of this protocol. Nektar Therapeutics may transition to reporting of SAEs via electronic data capture (EDC) while the study is ongoing. If this occurs, all sites will receive documented instructions regarding how to enter SAEs into EDC. If the study were to transition to reporting of SAEs in EDC, sites would continue to submit SAEs via email or Safety Fax as a backup system should there be EDC system access issues.

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

All SAEs will be followed as described in Section 7.8.

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

7.8 Serious AE Follow-up

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

- The event resolves.
- The event has stabilized.
- The event returns to baseline, if a baseline value is available.
- It is unlikely that any additional information can be obtained (eg, 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. Disease progression should not be reported as an AE or SAE. In some patients, disease progression may result in clinical manifestations (eg, pleural effusion) that meet “seriousness” criteria (eg, hospitalization). These clinical manifestations may be reported as non-fatal SAEs.

For all SAEs assessed as clinical manifestations associated with fatal disease progression, the following criteria will apply:

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

Deaths that are attributed solely to disease progression by the Investigator should not be reported as SAEs.

7.10 Immune-mediated AEs (IMAEs) and Other Monitored Events

Immune-mediated AEs (imAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. imAEs can include events with an alternate etiology, which were exacerbated by the induction of autoimmunity. Investigators should use clinical judgment characterizing an AE as immune mediated, including the requirement for steroid treatment, and are encouraged to rule out neoplastic, infectious, metabolic, toxic, or other etiologies to the extent possible, before characterizing an event as immune mediated. Nektar will internally review imAEs to determine their association with NKTR-214 or pembrolizumab.

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

Management Algorithm for Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a clinical diagnosis of exclusion that usually presents with a constellation of symptoms associated with cytokine side effects such as persistent fever, hypotension, hypoxia in association with/without tachypnea, headache, rash, tachycardia, or organ toxicity with varied manifestation. For confirmed cases of CRS or suspected CRS Grade 3 or higher, the Investigator should contact the Medical Monitor regarding treatment modifications or dose changes. A general guidance with algorithm for CRS management and reportability is provided in Appendix 4.

7.11 Adverse Events of Special Interest

The AEs listed below are considered “adverse events of special interest” (AESI). Regardless of the assessment of whether the AESI is serious or nonserious, all AESIs are required to follow the timeline for SAE reporting (within 24 hours of awareness as described in Section 7.7.) from the sites to Nektar Drug Safety: pharmacovigilance@nektar.com.

- CVA events (any grade; CVA Management Guidelines are provided in Appendix 2)

7.12 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 4 months after the last dose of all study drugs for female patients or 4 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. Female patients 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.

7.13 Potential Drug Induced Liver Injury

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

Potential drug induced liver injury is defined as:

1) Treatment-emergent ALT or AST > 3 times ULN, and
2) Total bilirubin > 2 times ULN or clinical jaundice, without initial findings of cholestasis (elevated serum alkaline phosphatase), and
3) No other immediately apparent possible causes of elevated liver enzymes and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.14 Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Events (Section 1.1). Clinical laboratory tests will be performed by local and central laboratories. Samples for clinical laboratory tests must be drawn within 72 hours prior to dosing. Clinical laboratory tests will be performed by a local laboratory and the data will be reviewed by the Investigator or a qualified Sub-Investigator. Additional clinical laboratory tests may be ordered and performed at the local laboratory at the Investigator's or qualified Sub Investigator's discretion. Testing for PK [redacted] will be performed by a designated central laboratory.

The Investigator or qualified Sub-Investigator will review all clinical laboratory test results for clinical significance. Any laboratory result deemed clinically significant (ie, 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 (see Section 1.1). Full physical examinations (that 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) should be conducted at screening, and Days 1, 3 and 8 of Cycle 1. In Cycle 2 and beyond, full physical examinations are conducted on Day 1 of each cycle, and EOT. 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. Weight is to be reported at each dosing visit (for weight changes of ± 10% from baseline, recalculation of dose is not required), height at screening visit only.

7.16 Vital Signs

Vital sign measurements will be recorded according to the Schedule of Events (Section 1.1). Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure (supine position), oxygen saturation (on dosing days only), and temperature (oral preferred). 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 5.3.4.1.

7.17 Electrocardiograms

A screening 12-lead ECG must be done during the 28-day screening window prior to Cycle 1 Day 1. Patients must be resting quietly in the supine position for at least 5 minutes before the ECG collection. Each ECG will be submitted to a local ECG laboratory for interpretation.

The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance.

7.18 Echocardiograms

Standard ECHOs will be performed at screening or within 90 days of Day 1 Cycle 1 to assess cardiac function and LVEF according to the Schedule of Events (Section 1.1). 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 ECHO cannot be performed.

7.19 Pregnancy Tests

Serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) will be performed on women of childbearing potential during screening (anytime during 28-day screening window; ICF signature not required). Urine pregnancy tests will be performed on Day 1 of each cycle prior to dosing and at EOT. A negative pregnancy test result must be obtained before the administration of the study drug(s).

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

If a female patient becomes pregnant, administration of the study drug(s) must be discontinued immediately. Requirements for reporting a pregnancy are provided in Section 7.12.

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).

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 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 must be used to characterize each lesion at baseline and during follow-up. Imaging-based evaluation must 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 (eg, skin nodules). When lesions can be evaluated by both clinical examination and imaging, imaging evaluation must 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 must be obtained and utilized for measurement.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (eg, for body scans). CT portion of PET-CT is acceptable if RECIST 1.1 measurements can be done.

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 (eg, 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 16 provides the definitions of the criteria used to determine objective tumor response for target lesions.

Table 16: 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 17 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 17: 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]

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).

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.

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 assessments 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

Best overall response when confirmation of CR and PR is required is summarized in Table 18.

Table 18: 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

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 (8 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 will be summarized by dose cohort.

For the 1L NSCLC dose expansion cohort (Cohorts 2 and 3), all efficacy endpoints except overall survival will be analyzed using the response evaluable population. Certain efficacy endpoints will also be summarized for all treated patients as sensitivity analyses. All safety endpoints will be summarized using the safety population.

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

9.2 Determination of Sample Size

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

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

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

The Fleming 2-stage design (Fleming, 1982) framework will be used as a guide for the 1L NSCLC Expansion Cohorts 2, 3, 4, and 5. The total sample size for each 1L NSCLC expansion cohort (TPS <1%, TPS 1% to 49%, and TPS ≥ 50%) will be calculated based on a one-sided Type 1 error of 10% and a power of 90%. The 2-stage design provides an option to stop early for

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

Cohorts 2 and 3:

Approximately 58 response-evaluable first-line NSCLC patients may be enrolled in Cohort 2 (and in Cohort 3 if opened), including: Cohort 2.1/3.1: minimum 20 PD-L1 < 1%, Cohort 2.2/3.2: minimum 18 PD- L1 1% to 49%, and Cohort 2.3/3.3: minimum 20 PD-L1 ≥ 50%. Patients who are not response-evaluable and patients whose PDL-1 status is unable to be confirmed by central testing will be replaced (Table 19).

Table 19: True (Target) and Historic Objective Response Rate for First-line NSCLC by PD-L1 Categorization (Cohorts 2 and 3)

		Objective Response Rate (ORR) (%)		Sample Size[a] (Minimum Sample Size)			Futility		Efficacy		Reference for Historical ORR Assumption
Cohort	**Indication**	Historical	Target	N 1	N2	Total	S1	S2	T1	T2	
2.1	NSCLC 1L (PD-L1 < 1%)[b]	8	30	12	8	20	0	≤ 3	≥ 3	≥ 4	Carbone 2017 Garon 2015
2.2	NSCLC 1L (PD-L1 1% to 49 %)[b]	14	40	8	10	18	0	≤ 4	≥ 4	≥ 5	
2.3	NSCLC 1L (PD-L1 ≥ 50%)	25	55	11	9	20	≤ 3	≤ 7	≥ 6	≥ 8	

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

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

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

Cohorts 4 and 5

Based on safety and efficacy data from Cohorts 2 and 3, a decision may be made to open Cohorts 4 (1L nonsquamous NSCLC) and 5 (1L squamous NSCLC). Up to 63 response

evaluable patients may be enrolled in each of Cohorts 4 and 5, using a Fleming 2-stage design framework (see details in Statistical Analysis Plan). Patients who are not response-evaluable or who have insufficient biopsy material for PD-L1 assessment may be replaced.

9.3 Safety Monitoring

In addition to routine safety monitoring on AEs, lab test findings, ECG and vital signs, 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 as per charter at least quarterly during the study to review safety data from the dose optimization and dose expansion cohorts 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

In the dose optimization cohorts, patients who did not complete the DLT observation period for reasons other than a DLT will be replaced to provide the number of patients included for the dose escalation decision. In Dose Expansion Cohorts 2, 3, 4, and 5, patients who are not response-evaluable or who have insufficient biopsy material for PD-L1 assessment may be replaced.

In Amendment 6.0 and subsequent versions, first-line NSCLC patients who enroll in the study, but do not meet the eligibility criteria will be replaced.

9.5 Analysis Sets

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

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

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

Response-Evaluable Population: Patients who have received at least 1 dose (or partial dose) of study drug, have measurable disease (per RECIST 1.1) at baseline, and have at least 1 scheduled postbaseline assessment of tumor response (earliest assessment at 9 weeks ± 1 week).

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 and presented in data listings.

9.6.2 Safety

One of the primary endpoints of the study is to determine the MTD of NKTR214 in combination with pembrolizumab. AEs and toxicity for the dose optimization cohorts will be evaluated according to NCI CTCAE version 5.0. Adverse events and toxicity for the dose expansion cohorts will be evaluated according to NCI CTCAE version 5.0. 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 evaluable patients.

Treatment emergent AEs (TEAEs) will be summarized by latest MedDRA preferred term, system organ class, NCI CTCAE version 5.0 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. 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 for the following efficacy outcomes:

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

The primary efficacy measurement is the confirmed ORR in the response-evaluable patients per BICR by RECIST 1.1 based on data provided by BICR. The secondary endpoint is ORR by the Investigator's assessment using the response-evaluable population. The number and percentage of patients with CR or PR as their best overall response will be calculated. The 95% confidence interval (CI) will be calculated using the exact binomial method. In addition, the ORR analysis will be performed on the response evaluable population. All tumor assessments and response data will be listed. The best overall response (BOR) of CR, PR, SD and PD 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. 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 (≥ 8 weeks), will be summarized similarly to ORR using the response evaluable population and all treated patients. Additionally, CBR at 18 weeks (CBR18) and CBR at 27 weeks (CBR27), defined as confirmed CR, confirmed PR, or SD for ≥ 18 weeks or ≥ 27 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 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 all treated patients.

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

9.6.4 Immunogenicity

Validated methods to detect anti-NKTR-214, anti-IL-2, and anti-pembrolizumab ADA will be used to analyze the immunogenicity samples. Samples will be analyzed by multi-tiered ADA testing. Immunogenicity samples will be first tested with screening assays. Putative positive samples will then be analyzed in competition assays to confirm positivity. Confirmed anti-NKTR-214 ADA positive samples will be tested further in a PEG-immunocompetition assay to determine the antibody specificity of the reactivity to the PEG or non-PEG (IL-2, linker) moiety of NKTR-214. Confirmed positive samples from anti-pembrolizumab, anti-NKTR-214, and anti-IL-2 ADA assays will then be tested to obtain a titer. Samples confirmed to be positive for anti-pembrolizumab, anti-NKTR-214, and anti-IL-2 ADA may also be tested for neutralizing activity using validated assays.

Blood samples designated for assessments (eg, immunogenicity, PK, [redacted]) from the same collection time point may be used interchangeably for analyses, if required (eg, insufficient volume for complete assessment, to follow-up on suspected immunogenicity related AE, etc.).

[redacted]

9.6.6 Pharmacokinetics

Plasma concentrations of NKTR-214 and its metabolites will be measured using validated or qualified method(s). Methods for calculating PK parameters will be described in a PK Analysis Plan. 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 feasible. Plasma concentration-time data and PK parameters will be tabulated and summarized with descriptive statistics. Select PK parameter values may be evaluated for correlations with select safety and response measurements for assessment of exposure-response relationships. Pharmacokinetic data from this study may also be pooled with data from other clinical studies for the purpose of population PK modeling and/or exposure-response analyses, which would be prospectively described in one or more analysis plans and reported separately from the Study 16-214-05 clinical study report.

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 unevaluable.

All protocol deviations and the reasons for such deviations are to be 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.

If a patient continues study treatment beyond disease progression, a separate ICF will be signed at that time.

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 (eg, 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) (eg, 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.

14.0 PUBLICATION POLICY

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

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

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APPENDIX 1: CLINICAL LABORATORY TESTS

Local Clinical Laboratory Tests Obtained Prior to NKTR-214 Study Drug Administration

Laboratory Tests Required for Treatment Decisions		
• AST (SGOT) • ALT (SGPT) • Serum Creatinine • Blood urea nitrogen (BUN) or urea	• Total bilirubin • Sodium • Potassium	• Pregnancy test (for WCBP) • Any additional clinically-relevant test related to individual patient monitoring[a]

[a] Particularly for patients with baseline comorbidities

Laboratory tests must be assessed by a local laboratory within 24 hours, or as soon as locally feasible, prior to each NKTR-214 study drug administration.

Clinical Laboratory Test Panel

<table>
<tr><th colspan="4">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Chemistry</th><th colspan="2">Serology (Screening Only)</th></tr>
<tr><td rowspan="2">• 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="2">• 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 (optional)
• Blood urea nitrogen (BUN) or urea
• 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>Coagulation
• Partial thromboplastin time (PTT)
• Prothrombin time (PT)</td><td colspan="2">Additional Labs
• Creatine kinase
• Serum or urine pregnancy (HCG) for WCBP
• Thyroid stimulating hormone (TSH)
• Free thyroxine (T4)
• Free or total triiodothyronine (T3)
• Lipase
• Amylase</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>

APPENDIX 2: CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM

Table 20 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 20: Cerebrovascular Accident Adverse Event Management Algorithm

CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM **This guideline pertains to all patients.**	
For unexplained neurological symptoms (such as hemiparesis, confusion, dysarthria, or visual disturbances) which may be associated with CVA: **perform neurological imaging, (MRI including diffusion-weighted imaging (DWI) preferred) 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 preferred unless contraindicated), regardless of neurological symptoms (eg, cryptogenic CVA): • Discontinue study treatment For suspected TIA without clear alternative etiology: • 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, coagulation studies including D-dimer, complete blood count with differential, serum blood urea nitrogen, and creatinine. [redacted]
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.

APPENDIX 3: WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PATIENTS OF CHILDBEARING POTENTIAL

At a minimum, patients must agree to use 2 effective methods of contraception, with 1 method being highly effective and another method from the list below during study duration for female patients and until the end of relevant systemic exposure, defined as 4 months following the last dose of study treatment. (Note: Local laws and regulations may require use of alternative and/or additional contraception methods).

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of <1% per year when used consistently and correctly.[a]
• **Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation** • oral • intravaginal • transdermal
• **Progestogen-only hormonal contraception associated with inhibition of ovulation** • oral • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Hormonal methods of contraception including vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS) • Intrauterine device (IUD) • Bilateral tubal occlusion
• Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient. • It is not necessary to use any other method of contraception when complete abstinence is elected. • WCBP patients who choose complete abstinence must continue to have pregnancy tests, as specified in Section 1.1. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WCBP patients chose to forego complete abstinence.
NOTE: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.

Less Acceptable Methods of Contraception[a]
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

CONTRACEPTION GUIDANCE FOR MALE PATIENTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL

Male patients with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the Investigator.
- Male patients are required to use a condom for study duration and until end of relevant systemic exposure defined as 4 months after the end of study treatment for male patients treated with NKTR-214/pembrolizumab.
- WCBP who are partners of males participating in the study to consider use of highly effective methods of contraception, listed in the table above, until the end of relevant systemic exposure, defined as 3 months after the end of treatment in male patients treated with NKTR-214/pembrolizumab.
- Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 4 months after the end of study treatment for male patients treated with NKTR-214/pembrolizumab.
- Refrain from donating sperm for the duration of the study treatment and until 4 months after the end of study treatment for male patients treated with NKTR-214/pembrolizumab.

Guidance for collection of Pregnancy Information is provided in Section 7.12.

APPENDIX 4: CYTOKINE RELEASE SYNDROME (CRS) MANAGEMENT ALGORITHM

The following treatment management guidelines are provided for general guidance. These guidelines should not substitute for a more individualized, tailored approach to managing a patient experiencing CRS (see Section 5.14.2).

CRS Management Measures/Algorithm

As a general principle, differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

For patients with suspected CRS:

- For Grade 1 or Grade 2 events, implement supportive care, including management of isolated symptoms based on institutional practices.
- Consider admitting the patient for monitoring and providing supportive care, including management of isolated symptoms based on institutional practices and protocol management guidelines (eg, hydration management guidelines, Section 5.3.4.2).
- For patients with a persistent or worsening clinical condition after initial treatment of CRS, reevaluate for other contributing conditions. It is particularly important to reassess the patient for coexisting infections, and cardiac, pulmonary, thromboembolic and other complications.

Grading Assessment per CTCAE v.5.0		**Treatment Measures Recommended**
Grade 3 CRS	- Hypotension managed with one pressor - Hypoxia requiring > 40% O_2	- Vasopressin administration should be considered if the hypotensive event is refractory to >3L of fluid resuscitation - Oxygen therapy (nasal canula, non-invasive positive pressure ventilation, etc.) for respiratory symptoms with consideration of intubation for a patient with severe respiratory manifestations - Supportive care for renal, hepatic and other organ function deteriorations - Steroid therapy should be considered (eg, hydrocortisone 100 mg every 8 hours, dexamethasone 10 mg up to 4 times daily, 1-2 mg/kg/day methylprednisone IV or PO equivalent) - High dose steroid (eg, solumedrol 2 mg/kg up to 1 gram daily for 3 days) may be considered for severe CRS that failed to respond after repetitive steroid treatments - For severe CRS cases that require simultaneously aggressive management of hypotension, oxygenation, and cardiac telemetry, consult Intensivist for ICU evaluation
Grade 4 CRS	- Life-threatening consequences - Pressor or ventilatory support indicated	