Nektar Therapeutics

CLINICAL PROTOCOL

Protocol No.	17-214-09 / CA045002
Title:	A Phase 3 Randomized Open Label Study to Compare NKTR-214 Combined with Nivolumab to the Investigator's Choice of Sunitinib or Cabozantinib in Patients with Previously Untreated Advanced Renal Cell Carcinoma
Version:	Amendment 3.0
Date:	19 October 2021
Supersedes:	Amendment 2.0, 03 February 2020
US IND No.:	140913
Ex US:	Non-IND
Eudra CT No.:	Not applicable
Investigational Product:	Bempegaldesleukin (NKTR-214) in combination with nivolumab
Indication:	Treatment of advanced renal cell carcinoma
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA
Sponsor's Medical Contact and Study Medical Monitor:	[redacted]

CONFIDENTIALITY STATEMENT

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PRINCIPAL INVESTIGATOR COMMITMENT

Protocol No.	17-214-09 / CA045002
Title:	A Phase 3 Randomized Open Label Study to Compare NKTR-214 Combined with Nivolumab to the Investigator's Choice of Sunitinib or Cabozantinib in Patients with Previously Untreated Advanced Renal Cell Carcinoma
Version, Date:	Amendment 3.0, 19 October 2021
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

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:

Institution:

Address:

PROTOCOL APPROVAL PAGE

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Signature

Printed Name: [redacted]

Position:

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ABBREVIATIONS

Abbreviation or Term	Definition
ACE	angiotensin-converting-enzyme
ADA	anti-drug antibodies
AE	adverse event
AEC	absolute eosinophil count
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
bempegaldesleukin	International Nonproprietary Name (INN) for NKTR-214
BICR	blinded independent central review
BTLA	B- and T-lymphocyte attenuator
C_{avgss}	simulated steady state average concentration
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CMH	Cochran-Mantel Haenszel
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRF	case report form
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
CYP3A4	cytochrome P450 3A4
D5W	dextrose 5% in water for injection
DCI	data collection instrument(s)
DILI	drug-induced liver injury

Abbreviation or Term	Definition
DMC	Data Monitoring Committee
DOAC	direct oral anticoagulation
DOR	duration of response
DRS	disease-related symptoms
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
ECG	electrocardiogram
ECLA	electrochemiluminescence assays
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D-3L	3-level version of the EuroQol Group's EQ-5D
EU	European Union
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FKSI-19	Functional Assessment of Cancer Therapy (FACT) Symptom Index for Kidney Cancer
FSH	follicle-stimulating hormone
g	gram
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCRU	health care resource utilization
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
ICOS	inducible T-cell co-stimulator

Abbreviation or Term	Definition
IEC	independent ethics committee
IFN-α	interferon-alpha
IFN- γ	interferon gamma
IHC	immunohistochemistry
IL-2	interleukin-2. For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule.
IL-2Rβγ	IL-2 receptor beta gamma
imAE	immune-mediated adverse event
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	institutional review board
IRT	Interactive Response Technology
ITT	intent-to-treat
IV	intravenous(ly)
kg	kilogram
LDH	lactate dehydrogenase
LFT	liver function test
LMWH	low molecular weight heparin
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute(s)
mL	milliliter
mm Hg	millimeters of mercury
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

Abbreviation or Term	Definition
NE	not evaluable
NK	natural killer
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PE	pulmonary embolism
PEG	polyethylene glycol
PET	positron emission tomography
PFS	progression-free survival
PFS2	PFS after the next line of treatment
PK	pharmacokinetic(s)
po	orally
PPK	population pharmacokinetic
PR	partial response
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
q2w	every 2 weeks
q3w	every 3 weeks
QTcF	Fridericia's corrected QT interval
R&D	Research and Development
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-2	recombinant human interleukin 2. For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule.
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
sCD25	soluble CD25

Abbreviation or Term	Definition
SD	stable disease
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TME	tumor microenvironment
Treg	regulatory T cell
TSE	treatment side effects
TTR	time to response
UK	United Kingdom
ULN	upper limit of normal
UPCR	urine protein creatinine ratio
US, USA	United States of America
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WOCBP	women of childbearing potential

1.0 STUDY SYNOPSIS

Title of Study:	A Phase 3 Randomized Open Label Study to Compare NKTR-214 Combined with Nivolumab to the Investigator's Choice of Sunitinib or Cabozantinib in Patients with Previously Untreated Advanced Renal Cell Carcinoma
Sponsor:	Nektar Therapeutics
Name of Finished Product(s):	NKTR-214 drug product Opdivo® Sutent® Cabometyx®
Name of Active Ingredient(s):	bempegaldesleukin (NKTR-214) drug substance Nivolumab (anti-PD-1) Sunitinib malate Cabozantinib (S)-malate
Phase of Development:	Phase 3
Objectives:	The primary objectives are: • To compare the objective response rate (ORR) by blinded independent central review (BICR) assessment using modified Response Evaluation Criteria in Solid Tumors (mRECIST; Appendix 9) 1.1 of NKTR-214 combined with nivolumab to that of tyrosine kinase inhibitor (TKI) monotherapy (sunitinib or cabozantinib) in International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate- or poor-risk patients with previously untreated advanced renal cell carcinoma (RCC) • To compare the ORR by BICR using mRECIST 1.1 of NKTR-214 combined with nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC all-risk patients with previously untreated advanced RCC • To compare the overall survival (OS) of NKTR-214 combined with nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC intermediate- or poor-risk patients with previously untreated advanced RCC • To compare the OS of NKTR-214 combined with nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC all-risk patients with previously untreated advanced RCC The key secondary objectives are: • To compare the progression-free survival (PFS) by BICR using mRECIST 1.1 of NKTR-214 combined with nivolumab to TKI monotherapy (sunitinib or cabozantinib) in IMDC intermediate- or poor-risk patients with previously untreated advanced RCC • To compare the PFS by BICR using mRECIST 1.1 of NKTR-214 combined with nivolumab to TKI monotherapy (sunitinib or cabozantinib) in IMDC all-risk patients with previously untreated advanced RCC The other secondary objectives are: • To estimate the incidence of adverse events (AEs) of NKTR-214 combined with nivolumab versus TKI monotherapy (sunitinib or cabozantinib) in patients with previously untreated advanced RCC

Objectives:	• To evaluate whether programmed cell death ligand 1 (PD-L1) expression on tumor cells (< 1% vs ≥ 1%) using the PD-L1 immunohistochemistry (IHC) 28-8 pharmDx assay is a predictive biomarker for ORR, PFS, and OS in patients with previously untreated advanced RCC • To characterize changes in cancer-related symptoms and quality-of-life in patients with previously untreated advanced RCC using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy (NCCN/FACT) Symptom Index for Kidney Cancer (FKSI-19) [redacted]
Duration of Treatment:	Patients will be treated until a maximum of 2 years (Arm A only), disease progression per mRECIST 1.1 in the absence of clinical benefit as determined by the Investigator, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, patient decision to discontinue treatment or withdraw consent, loss to follow-up, or termination of the study by the Sponsor. Treatment may continue beyond progression if the patient is receiving clinical benefit as determined by the Investigator.
Study Population:	Patients aged 18 years and older with advanced or metastatic, histologically confirmed RCC (advanced RCC) with a clear-cell component, who have not received prior therapy for the treatment of RCC.
Number of Patients (Planned):	Approximately 600 patients (including at least 500 patients with IMDC intermediate- and poor-risk and approximately 100 patients with IMDC favorable risk) with previously untreated advanced RCC will be randomized (300 per arm).
Number of Study Sites:	123 sites
Countries/Regions:	Global

Study Design:	This is a multicenter, randomized, open label, Phase 3 study that will evaluate the efficacy and safety of NKTR-214 combined with nivolumab compared with the Investigator's choice of a TKI, either sunitinib or cabozantinib, in patients with previously untreated advanced RCC. Patients will be randomized in a 1:1 ratio to one of the two treatment arms: • **Arm A**: NKTR-214 0.006 mg/kg intravenous (IV) every 3 weeks (q3w) combined with nivolumab 360 mg IV q3w • **Arm B**: The Investigator's choice of either one of the following treatments o Sunitinib 50 mg orally (po) once daily for 4 weeks followed by 2 weeks off **OR** o Cabozantinib 60 mg po once daily The treatment period of the study is divided into multiple treatment cycles with associated evaluations and procedures. One cycle of treatment is defined as 6 weeks. This study is divided into a Screening period, a Treatment period, and a Long-Term Follow-Up period, which will continue until withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. Randomization will be stratified by: • The IMDC prognostic score (0 [favorable risk] vs 1-2 [intermediate risk] vs 3-6 [poor risk]) • TKI choice (sunitinib or cabozantinib) The overall alpha for this study is 0.05, which is split with 0.001 to evaluate ORR in IMDC intermediate- or poor-risk and IMDC all-risk populations and 0.049 to evaluate OS in IMDC intermediate- or poor-risk and IMDC all-risk populations. All alpha levels are two-sided. The test in IMDC all-risk population is gated by the one in IMDC intermediate- or poor-risk population for both ORR and OS. That is, ORR in IMDC all-risk population will not be tested unless ORR in IMDC intermediate- or poor-risk population is statistically significant; and similarly, OS in IMDC all-risk population will not be tested unless OS in IMDC intermediate- or poor-risk population is statistically significant. In addition, a fallback approach will be used to reallocate alpha from ORR to OS. If ORR is significant in IMDC intermediate- or poor-risk and IMDC all-risk populations, the alpha of 0.001 will be passed to OS. OS in IMDC intermediate- or poor-risk population can then be tested at 0.05 (instead of 0.049) level. If it is significant, the alpha of 0.05 will be passed to OS in IMDC all-risk population.
Key Eligibility Criteria:	All eligibility criteria are listed in Section 4.0.
Test Product, Dose and Mode of Administration:	• NKTR-214 administered IV over 30 (± 5) minutes at a starting dose of 0.006 mg/kg q3w • Nivolumab administered IV over 30 (± 5) minutes at a 360 mg flat dose q3w (Nivolumab administration should start at least 30 minutes after the end of the NKTR-214 administration).
Comparator Product, Dose and Mode of Administration:	Sunitinib 50 mg po once daily for 4 weeks followed by 2 weeks off **OR** Cabozantinib 60 mg po once daily

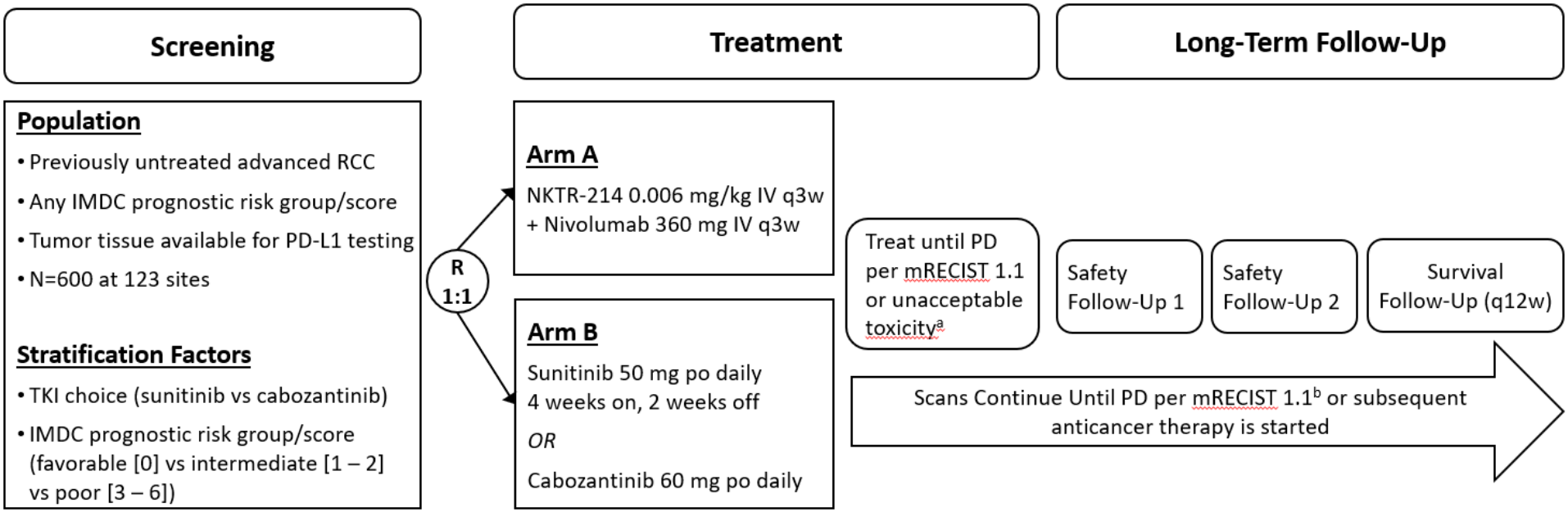
Biomarkers:	For all patients: Tumor tissue will be collected during the Screening period for characterization of PD-L1 expression, immune system-related genes, and proteins and mutations in cancer-related genes. Optional tumor biopsies may occur on study in Cycle 1 and at disease progression. For Arm A only: Biomarkers will be assessed from PK blood samples collected on study. [redacted]CVA biomarker samples will be obtained from patients from whom a Cycle 1 Day 1 biomarker sample has been collected (see Table 6, Section 5.10.3, and Appendix 6).
Pharmacokinetic Evaluation:	Blood samples for PK analyses will be collected from patients randomized to Arm A. Serial blood samples will be collected at multiple scheduled sampling times to measure plasma concentrations of NKTR-214 and its metabolites using validated method(s). Blood samples will also be collected for the measurement of nivolumab concentrations. Population PK will be used to estimate the exposure parameters.
Efficacy Evaluation:	The primary efficacy measurements are ORR by BICR in the IMDC intermediate- or poor-risk population and IMDC all-risk population, and OS in the IMDC intermediate- or poor-risk population and IMDC all-risk population. The key secondary efficacy measurements are PFS by BICR in the IMDC intermediate- or poor-risk population and IMDC all-risk population. Tumor measurements should be performed every 9 weeks (± 7 days) from randomization through (and inclusive of) Week 54 and then every 12 weeks (± 7 days). Tumor assessment schedule will be maintained regardless of dose delays. Tumor assessments will continue until both BICR and Investigator's assessments of tumor images have determined progression. Patients who are receiving study treatment beyond progression should continue scans until the criteria for treatment discontinuation are met and BICR-assessed progression has occurred. Tumor assessments are no longer required if subsequent anticancer therapy is started, even if the patient has not yet progressed.
Safety Evaluation:	Assessment of safety will be determined by an ongoing review of the following: • incidence of AEs, including serious AEs (SAEs) • clinical laboratory tests (blood and urine sampling) • vital signs • physical examinations

Statistical Methods	**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. **Efficacy:** ORR is defined as the percentage of patients with a confirmed best overall response of complete response (CR) or partial response (PR) by mRECIST 1.1 (Appendix 9) per BICR. As a primary efficacy endpoint, the ORR in IMDC intermediate- or poor-risk and IMDC all-risk populations will be compared using a stratified Cochran-Mantel Haenszel (CMH) test at an alpha level of 0.001. The ORR difference between the two treatment arms with its 95% and 99.9% confidence intervals (CI) will be reported. Overall survival (OS) is defined as the time between the date of randomization and the date of death due to any cause. 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. As a primary efficacy endpoint, OS in IMDC intermediate- or poor-risk and all-risk population will be evaluated at an alpha level of 0.049. The CHW version of the stratified log-rank test statistic with pre-specified weights will be used to compare OS between the 2 treatment arms. A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the hazard ratio and corresponding 95% CI. The Kaplan-Meier method will be used to further summarize OS, including Kaplan-Meier curves, medians with corresponding 95% CIs. The OS rates at 12 and 24 months will also be estimated. Progression-free survival is defined as the time between the date of randomization and the first date of documented tumor progression using mRECIST 1.1 per BICR or death due to any cause, whichever comes first. As the secondary efficacy endpoint, PFS in IMDC intermediate- or poor-risk and IMDC all-risk populations will be analyzed in a similar manner as OS; a Fleming-Harrington test will be used due to the delayed effect observed in another nivolumab study of patients with RCC (Motzer 2018b). The total planned sample size is 600 patients and it is estimated that at least 500 IMDC intermediate- or poor-risk and approximately 100 IMDC favorable-risk patients with previously untreated advanced RCC will be randomized into the two treatment arms (NKTR-214 combined with nivolumab vs TKIs) in a 1:1 ratio. At an interim analysis when at least 156 OS events in IMDC intermediate- or poor-risk population are observed, all primary endpoints will be tested. Two parallel sequential tests will be conducted: (1) ORR in IMDC intermediate- or poor-risk and IMDC all-risk populations at $\alpha = 0.001$ and (2) OS in IMDC intermediate- or poor-risk and IMDC all-risk populations at $\alpha = 0.01$. Within (1), ORR in IMDC all-risk population will only be tested at 0.001 if ORR in IMDC intermediate- or poor-risk is statistically significant at 0.001. Within (2), OS in IMDC all-risk population will only be tested at 0.01 if OS in IMDC intermediate- or poor-risk is statistically significant at 0.01. If OS in the IMDC intermediate-or poor-risk population is not statistically significant, conditional power will be calculated based on this population. The adaptive method in Liu and Hu (2016) and Mehta and Pocock (2011) will be used to determine the number of OS events in IMDC intermediate- or poor-risk population needed to target approximately 85% to 90% conditional power for the final analysis. If OS in IMDC intermediate- or poor-risk is statistically significant, but not in the IMDC all-risk population, then the conditional power will be calculated for the IMDC all-risk population. The adaptive method in Liu and Hu (2016), and Mehta and Pocock (2011) will be used to determine the number of OS events

	in IMDC all-risk population needed to target approximately 85% to 90% conditional power for the final analysis. The minimum and maximum number of OS events in IMDC intermediate- or poor-risk population for the final analysis are 200 and 308, respectively. The minimum event size is calculated to achieve 90% power with alpha = 0.049 (two-sided) assuming an exponential distribution in each treatment arm and a hazard ratio = 0.63 with median OS for the TKI arm of 26 months in IMDC intermediate- or poor-risk population. The maximum event size is determined based on the minimum clinically meaningful effect. **Safety:** Safety assessments will include AEs, clinical laboratory tests, vital signs, and physical examinations. All safety data will be summarized for the Safety Population using descriptive statistics by treatment arm.

1.1 Study Schematic

Figure 1: Study Schematic



IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IV = intravenous(ly); mRECIST 1.1 = Modified Response Evaluation Criteria in Solid Tumors version 1.1; PD = progressive disease; PD-L1 = programmed cell death ligand 1; po = oral(ly); q12w = every 12 weeks; q3w = every 3 weeks; R = randomized; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor

a. Maximum treatment duration of 2 years from Cycle 1 Day 1 (Arm A only); see Section 5.4.3 for other protocol-defined reasons for treatment discontinuation.

b. Tumor assessments will continue until both BICR and Investigator's assessments of tumor images have determined progression.

1.2 Schedule of Events

Table 1: Screening Schedule of Events

Procedure [a]	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response System to obtain patient number. Must occur prior to any protocol-specific study assessments.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization.
Medical History	X	Assessment of signs and symptoms and all medical history, including smoking history and alcohol use
International Metastatic RCC Database Consortium (IMDC) Prognostic Score	X	See Appendix 1.
Tumor Sample	X	All patients must have tumor tissue available, preferably most recent archival sample, from a site not previously irradiated and with no intervening treatment between time of acquisition and randomization or A fresh pre-treatment biopsy obtained during the Screening period. Tissue may be from a core biopsy, punch biopsy, excisional biopsy, or surgical specimen; fine needle aspiration and other cytology samples are not acceptable. A formalin-fixed paraffin-embedded block or unstained slides sectioned from a block within 3 months prior to randomization (minimum of 8 slides, preferably 20 slides). Please refer to Section 5.10.1 for further details.
Safety Assessments		
Full Physical Examination and Vital Signs	X	Height and weight Vital Signs: blood pressure, heart rate, temperature, and pulse oximetry Within 14 days from randomization. See Sections 8.16 and 8.17.
Karnofsky Performance Status	X	Within 14 days from randomization. See Appendix 2.
Concomitant Medication Use	X	Document all medication (including vaccine) use within 30 days prior to randomization. Assess within 14 days prior to randomization.

Abbreviations used in this table appear on the final page of Table 4.

Table 1: Screening Schedule of Events (Contd)

Procedure [a]	Screening Visit	Notes
SAE Assessment	X	Collected from time of consent. See Section 8.7 for further details.
ECG	X	12-lead within 14 days from randomization. See Section 8.18 for further details.
Echocardiogram or MUGA	X	Left Ventricular Ejection Fraction > 45% scan test within 60 days prior to randomization required for eligibility. The Investigator should also evaluate patients with any significant abnormalities on echocardiogram or MUGA and use best clinical judgment for decisions regarding treatment on study.
Laboratory Tests		
Clinical Laboratory Testing (central lab)	X	All laboratory assessments to be performed within 14 days prior to randomization. Refer to Appendix 3 for a list of required laboratory assessments and Section 8.15 for further details.
Urinalysis (central lab)	X	All laboratory assessments to be performed within 14 days prior to randomization. If proteinuria is observed (UPCR ≥ 1.0 [≥ 113 mg/mmol]), measurement of 24-hour urine protein is required
Pregnancy Test	X	Serum or urine test (minimum sensitivity 25 IU/L or equivalent units of hCG) in WOCBP to be performed within 28 days prior to randomization.
Tumor Assessment		
Body Imaging	X	Contrast-enhanced CT of the chest, contrast-enhanced CT or MRI of the abdomen, pelvis, and all other known and suspected sites of disease within 28 days prior to randomization. See Section 7.2 if patient has contraindications to contrast CT or MRI. Bone scans may be collected per local standards, if clinically indicated. Digital photography should be performed and submitted, if clinically indicated. See Section 7.0 for further details.
Brain Imaging	X	MRI of the brain without and with contrast is required for all patients at baseline within 28 days prior to randomization. See Section 7.2 if patient has contraindications to contrast MRI. See Section 7.0 for further details.
Outcomes Research Assessments		
FKSI-19	X	Within 28 days from randomization. See Section 7.6 for further details.
EQ-5D-3L	X	Within 28 days from randomization. See Section 7.6 for further details.

a. Assessments that occur outside of protocol-specified windows (e.g., for holidays, travel issues, insurance issues) may be acceptable on a case-by-case basis after review by the Medical Monitor.

Abbreviations used in this table appear on the final page of Table 4.

Table 2: On-Treatment Schedule of Events for Arm A

Procedure[a]	Arm A NKTR-214 0.006 mg/kg IV q3w and Nivolumab 360 mg IV q3w Cycle = 6 Weeks							Notes
	Cycle 1					Cycle 2 and all subsequent cycles		
	Day 1	Day 3 (–1 day)	Day 5 (± 1 day)	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
Study Drug								
Randomize	X							
Administer Study Drug	X				X	X	X	The first dose should be administered within 5 calendar days following randomization. NKTR-214 0.006 mg/kg IV q3w + Nivolumab 360 mg IV q3w Refer to Section 5.4.1 for sequential dosing instructions. If the IV study drug administration is delayed, the procedures scheduled for that visit should be performed with the delayed visit for drug administration (does not apply to tumor assessments; see Body Imaging below).
Administer IV fluids	X				X	X	X	May be withheld if deemed in the best interest of the patient by the Investigator Refer to Section 5.4.2.2 for further details.
Review hydration guidelines with patient	X				X	X	X	Applicable only while NKTR-214 is administered

Abbreviations used in this table appear on the final page of Table 4.

Table 2: On-Treatment Schedule of Events for Arm A (Contd)

Procedure[a]	Arm A NKTR-214 0.006 mg/kg IV q3w and Nivolumab 360 mg IV q3w Cycle = 6 Weeks							Notes
	Cycle 1					Cycle 2 and all subsequent cycles		
	Day 1	Day 3 (–1 day)	Day 5 (± 1 day)	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
Oral Hydration Follow-up	X^1				X^1	X^2	X^2	X^1 = Between 2 and 4 days following the first 2 administrations of NKTR-214 in Cycle 1, 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 compliance and symptoms from the discussion. X^2 = For subsequent NKTR-214 administrations in Cycle 2 and beyond, oral hydration follow-up should be conducted as clinically indicated between 2 and 4 days following NKTR-214 administration (see Section 5.4.2.2).
Safety Assessment								
Targeted Physical Examination, Weight, Vital Signs	X	VW	VW	VW	VW	X	VW	Vital Signs: blood pressure, heart rate, temperature Vital signs should be monitored at the following timepoints relative to study drug dose administrations: • Pre-dose (NKTR-214) • Within 30 minutes after administration of nivolumab VW = Vital Signs and Weight only
Karnofsky Performance Status	X					X		See Appendix 2.

Abbreviations used in this table appear on the final page of Table 4.

Table 2: On-Treatment Schedule of Events for Arm A (Contd)

Procedure[a]	Arm A NKTR-214 0.006 mg/kg IV q3w and Nivolumab 360 mg IV q3w Cycle = 6 Weeks							Notes
	Cycle 1					Cycle 2 and all subsequent cycles		
	Day 1	Day 3 (–1 day)	Day 5 (± 1 day)	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
AE Assessments (including SAEs)	Continuously							Record at each visit. Refer to Section 8.2 for the timing of AE/SAE collection.
Concomitant Medication Use	Continuously							Record at each visit.
Laboratory Tests								
Pregnancy Test (WOCBP Only)	X				X	X	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) is required within 24 hours prior to treatment.
Local laboratory tests prior to study drug dosing	X				X	X	X	Within 24 hours, or as soon as locally feasible, prior to study drug administration (See Section 8.15 and Appendix 3)
Clinical Laboratory Testing (central lab)	X			X	X	X	X	Refer to Section 8.15 for further details on clinical safety laboratory assessments (Hematology, Chemistry, Coagulation, and Additional Labs). See Appendix 3 for a list of required laboratory assessments. Central laboratory samples must be collected within 5 days of administering study drug(s). If central lab results will not be available in time, treatment may be based on local lab results (see Appendix 3 for details). All lab results must be assessed prior to administering study drug(s).

Abbreviations used in this table appear on the final page of Table 4.

Table 2: On-Treatment Schedule of Events for Arm A (Contd)

Procedure[a]	Arm A NKTR-214 0.006 mg/kg IV q3w and Nivolumab 360 mg IV q3w Cycle = 6 Weeks							Notes
	Cycle 1					Cycle 2 and all subsequent cycles		
	Day 1	Day 3 (–1 day)	Day 5 (± 1 day)	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
Urinalysis (central lab)	X					Y		See Appendix 3. Y = Performed every 3 cycles starting with Cycle 3 If clinically significant proteinuria (UPCR ≥ 2.0 [≥ 227 mg/mmol] or dipstick protein ≥ 3+) is observed, measurement of 24-hour urine protein is required.
Tumor Assessment								
Body Imaging	• Contrast-enhanced CT of the chest, contrast-enhanced CT or MRI of the abdomen, pelvis, and all known and suspected sites of disease should be performed every 9 weeks (± 7 days) from randomization through (and inclusive of) Week 54 and then every 12 weeks (± 7 days). See Section 7.2 if patient has contraindications to contrast CT or MRI. • Tumor assessment schedule is relative to the date of randomization and will be maintained regardless of dose delays. • Tumor assessments will continue until both BICR and Investigator's assessments of tumor images have determined progression. • Patients who are receiving study treatment beyond progression should continue scans until the criteria for treatment discontinuation are met and BICR-assessed progression has occurred. • Tumor assessments are no longer required if subsequent anticancer therapy is started, even if the patient has not yet progressed. • Use same imaging method as was used at screening. • Bone scans may be collected per local standards, if clinically indicated. Digital photography should be performed and submitted, if clinically indicated.							All study treatment decisions will be based on the Investigator's assessment of tumor images. See Section 7.0 for further details.

Abbreviations used in this table appear on the final page of Table 4.

Table 2: On-Treatment Schedule of Events for Arm A (Contd)

Procedure[a]	Arm A NKTR-214 0.006 mg/kg IV q3w and Nivolumab 360 mg IV q3w Cycle = 6 Weeks							Notes
	Cycle 1					Cycle 2 and all subsequent cycles		
	Day 1	Day 3 (–1 day)	Day 5 (± 1 day)	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
Brain Imaging	• Patients with a history of brain metastasis or neurological symptoms should have MRI with and without contrast. See Section 7.2 if patient has contraindications to contrast MRI. Performed on same schedule as body tumor assessments, and as clinically indicated • Tumor assessments will continue until both BICR and Investigator's assessments of tumor images have determined progression. • Patients who are receiving study treatment beyond progression should continue scans until the criteria for treatment discontinuation are met and BICR-assessed progression has occurred. • Tumor assessments are no longer required if subsequent anticancer therapy is started, even if the patient has not yet progressed. • Use same imaging method as was used at screening.							All study treatment decisions will be based on the Investigator's assessment of tumor images. See Section 7.0 for further details.
Pharmacokinetic and Biomarker Assessments								
[redacted]	[redacted]				[redacted]	[redacted]		[redacted]
NKTR-214 PK Blood Samples	X	X	X	X	X	Z		Z = Cycles 3, 6, 9, 12, and 15 only See Table 6 and Section 5.9 for further details.
Nivolumab PK Blood Samples	X				X	Z		Z = Cycles 3, 6, 9, 12, and 15 only See Table 6 and Section 5.9 for further details.
Tumor Tissue Sample								Optional Cycle 1 Day 14-21 and at disease progression. See Section 5.10.1 for further details.

Abbreviations used in this table appear on the final page of Table 4.

Table 2: On-Treatment Schedule of Events for Arm A (Contd)

Procedure[a]	Arm A NKTR-214 0.006 mg/kg IV q3w and Nivolumab 360 mg IV q3w Cycle = 6 Weeks							Notes
	Cycle 1					Cycle 2 and all subsequent cycles		
	Day 1	Day 3 (–1 day)	Day 5 (± 1 day)	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
[redacted]	[redacted]				[redacted]	[redacted]		[redacted]
Outcomes Research Assessments								
EQ-5D-3L	X				X	X	X	Patients should complete the assessment at the start of the clinic visit, prior to dosing and scheduled activities. Completed on Days 1 and 22 of every cycle through Cycle 4, and then on Day 1 of all subsequent cycles. See Section 7.6 for further details.
FKSI-19	X				X	X	X	
PRO-CTCAE	X				X	X	X	
Health Care Resource Utilization	X				X	X	X	Site staff will collect health care resource utilization data using the CRF.

a. Assessments and visits that occur outside of protocol-specified windows (e.g., for holidays, travel issues, insurance issues) may be acceptable on a case-by-case basis after review by the Medical Monitor.

Abbreviations used in this table appear on the final page of Table 4.

Table 3: On-Treatment Schedule of Events for Arm B

Procedure[a]	Arm B Cabozantinib 60 mg PO once daily (continuously) OR Sunitinib 50 mg PO once daily (4 weeks on treatment, followed by 2 weeks off treatment) Cycle = 6 Weeks					Notes
	Cycle 1			Cycle 2 and subsequent on-treatment visits		
	Day 1	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
Study Drug						
Randomize	X					
Dispense Study Drug	X		X	X	X	The first dose should be administered within 5 calendar days following randomization (see Section 5.4.1 for details). Cabozantinib or sunitinib study treatment and Pill Diary provided Day 1 of each cycle. Cabozantinib may also be dispensed on Day 22 of each cycle.
Pill Diary	X			X		
Safety Assessments						
Targeted Physical Examination, Weight, Vital Signs	X	VW	VW	X	VW	Vital Signs: blood pressure, heart rate, temperature VW = Vital Signs and Weight only
Karnofsky Performance Status	X			X		See Appendix 2.
AE Assessments (including SAEs)	Continuously					Record at each visit. See Section 8.2 for the timing of AE/SAE collection.
Concomitant Medication Use	Continuously					Record at each visit.

Abbreviations used in this table appear on the final page of Table 4.

Table 3: On-Treatment Schedule of Events for Arm B (Contd)

Procedure[a]	Arm B Cabozantinib 60 mg PO once daily (continuously) OR Sunitinib 50 mg PO once daily (4 weeks on treatment, followed by 2 weeks off treatment) Cycle = 6 Weeks					Notes
	Cycle 1			Cycle 2 and subsequent on-treatment visits		
	Day 1	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
Laboratory Tests						
Local laboratory tests prior to study drug dosing	X		X	X	X	Within 24 hours, or as soon as locally feasible, prior to study drug administration (See Section 8.15 and Appendix 3)
Clinical Laboratory Testing (central laboratory)	X	X	X	X	X	Refer to Section 8.15 for further details on clinical safety laboratory assessments (Hematology, Chemistry, Coagulation, and Additional Labs). See Appendix 3 for a list of required laboratory assessments. Central laboratory samples must be collected within 5 days before dispensing study drug. If central lab results will not be available in time, treatment decisions may be based on local lab results (see Appendix 3 for details). All lab results must be assessed prior to drug dispensation.
Urinalysis (central laboratory)	X			Y		Y = Performed every 3 cycles starting with Cycle 3 If clinically significant proteinuria is observed (UPCR ≥ 2.0 [≥ 227 mg/mmol] or dipstick protein ≥ 3+), measurement of 24-hour urine protein is required.

Abbreviations used in this table appear on the final page of Table 4.

Table 3: On-Treatment Schedule of Events for Arm B (Contd)

Procedure[a]	Arm B Cabozantinib 60 mg PO once daily (continuously) OR Sunitinib 50 mg PO once daily (4 weeks on treatment, followed by 2 weeks off treatment) Cycle = 6 Weeks					Notes
	Cycle 1			Cycle 2 and subsequent on-treatment visits		
	Day 1	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
Pregnancy Test (WOCBP Only)	X		X	X	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) is required within 24 hours before the first dose of study drug dispensation and before any assessments on Day 1 and Day 22 of each cycle.
Tumor Assessment						
Brain Imaging	• Patients with a history of brain metastasis or neurological symptoms should have MRI with and without contrast. See Section 7.2 if patient has contraindications to contrast MRI. Performed on same schedule as body tumor assessments, and as clinically indicated. • Tumor assessments will continue until both BICR and Investigator's assessments of tumor images have determined progression. • Patients who are receiving study treatment beyond progression should continue scans until the criteria for treatment discontinuation are met and BICR-assessed progression has occurred. • Tumor assessments are no longer required if subsequent anticancer therapy is started, even if the patient has not yet progressed. • Use same imaging method as was used at screening.					All study treatment decisions will be based on the Investigator's assessment of tumor images. See Section 7.0 for further details.

Abbreviations used in this table appear on the final page of Table 4.

Table 3: On-Treatment Schedule of Events for Arm B (Contd)

Procedure[a]	Arm B Cabozantinib 60 mg PO once daily (continuously) OR Sunitinib 50 mg PO once daily (4 weeks on treatment, followed by 2 weeks off treatment) Cycle = 6 Weeks					Notes
	Cycle 1			Cycle 2 and subsequent on-treatment visits		
	Day 1	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
Body Imaging	• Contrast-enhanced CT of the chest, contrast-enhanced CT or MRI of the abdomen, pelvis, and all known and suspected sites of disease should be performed every 9 weeks (± 7 days) from randomization through (and inclusive of) Week 54 and then every 12 weeks (± 7 days). See Section 7.2 if patient has contraindications to contrast CT or MRI. • Tumor assessment schedule is relative to the date of randomization and will be maintained regardless of dose delays. • Tumor assessments will continue until both BICR and Investigator's assessments of tumor images have determined progression. • Patients who are receiving study treatment beyond progression should continue scans until the criteria for treatment discontinuation are met and BICR-assessed progression has occurred. • Tumor assessments are no longer required if subsequent anticancer therapy is started, even if the patient has not yet progressed. • Use same imaging method as was used at screening. • Bone scans may be collected per local standards, if clinically indicated. Digital photography should be performed and submitted, if clinically indicated.					All study treatment decisions will be based on the Investigator's assessment of tumor images. See Section 7.0 for further details.
Biomarker Assessments						
Tumor Tissue Sample						Optional Cycle 1 Days 14-21 and at disease progression. See Section 5.10 for further details.

Abbreviations used in this table appear on the final page of Table 4.

Table 3: On-Treatment Schedule of Events for Arm B (Contd)

Procedure[a]	Arm B Cabozantinib 60 mg PO once daily (continuously) OR Sunitinib 50 mg PO once daily (4 weeks on treatment, followed by 2 weeks off treatment) Cycle = 6 Weeks					Notes
	Cycle 1			Cycle 2 and subsequent on-treatment visits		
	Day 1	Day 8 (−1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]
Outcomes Research Assessments						
EQ-5D-3L	X		X	X	X	Patients should complete the assessment at the start of the clinic visit, prior to dosing and scheduled activities. Completed on Days 1 and 22 of every cycle through Cycle 4, and then on Day 1 of the following cycles. See Section 7.6 for further details.
FKSI-19	X		X	X	X	
PRO-CTCAE	X		X	X	X	

Abbreviations used in this table appear on the final page of Table 4.

Table 3: On-Treatment Schedule of Events for Arm B (Contd)

Procedure[a]	Arm B Cabozantinib 60 mg PO once daily (continuously) OR Sunitinib 50 mg PO once daily (4 weeks on treatment, followed by 2 weeks off treatment) Cycle = 6 Weeks					Notes
	Cycle 1			Cycle 2 and subsequent on-treatment visits		
	Day 1	Day 8 (–1 day)	Day 22 (± 3 days)	Day 1 (± 3 days)	Day 22 (± 3 days)	
Health Care Resource Utilization	X		X	X	X	Site staff will collect the health care resource utilization data at each visit using the CRF.

a. Assessments and visits that occur outside of protocol-specified windows (e.g., for holidays, travel issues, insurance issues) may be acceptable on a case-by-case basis after review by the Medical Monitor.

Abbreviations used in this table appear on the final page of Table 4.

Table 4: Long-Term Follow-Up Schedule of Events

Procedure[a]	Safety Follow-Up Visit 1[b]	Safety Follow-Up Visit 2[b]	Survival Follow-Up[c] Every 12 Weeks (± 14 days)	Notes[d]
Safety Assessments				
Vital Signs	X	X		Blood pressure, heart rate, temperature Weight
AE and SAE Assessments	X	X	X	All AEs will be documented until 100 days after the last dose of all study drug(s). SAEs to be collected after the 100-day safety visit if the SAE is deemed to be related or residual toxicities are persisting. Patients will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible.
Karnofsky Performance Status	X	X		See Appendix 2.
Review of Subsequent Medications and Anticancer Therapy	X	X	X	In Survival Follow-up, subsequent anticancer treatment only. Additional subsequent anticancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression to subsequent anticancer therapies will be collected.
Laboratory Tests				
Pregnancy Test (WOCBP only)	X	X		Patients (WOCBP) will continue to follow instructions for methods of contraception through 5 months post treatment completion.
Clinical Lab Testing (central laboratory)	X	See Notes		During Safety Follow-up Visit 2 if toxicities are present. Refer to Section 8.15 for list of laboratory tests.
Pharmacokinetic and Biomarker Assessments				
Nivolumab PK Blood Samples (Arm A only)	X	X		See Section 5.9 for further details.

Abbreviations used in this table appear on the final page of the table.

Table 4: Long-Term Follow-Up Schedule of Events (Contd)

Procedure[a]	Safety Follow-Up Visit 1[b]	Safety Follow-Up Visit 2[b]	Survival Follow-Up[c] Every 12 Weeks (± 14 days)	Notes[d]
[redacted]	[redacted]	[redacted]		[redacted]
Tumor Tissue Sample	See Section 5.10			Optional upon disease progression
Efficacy Assessments				
Body Imaging	• Contrast-enhanced CT of the chest, contrast-enhanced CT or MRI of the abdomen, pelvis, and all known and suspected sites of disease. See Section 7.2 if patient has contraindications to contrast CT or MRI. • Imaging should continue every 9 weeks (± 7 days) from randomization through (and inclusive of) Week 54 and then every 12 weeks (± 7 days). • Tumor assessments will continue until both BICR and Investigator's assessments of tumor images have determined progression. • Patients who are receiving study treatment beyond progression should continue scans until the criteria for treatment discontinuation are met and BICR-assessed progression has occurred. • Tumor assessments are no longer required if subsequent anticancer therapy is started, even if the patient has not yet progressed. • Use same imaging method as was used at screening. • Bone scans may be collected per local standards, if clinically indicated. Digital photography should be performed and submitted, if clinically indicated.			All study treatment decisions will be based on the Investigator's assessment of tumor images. See Section 7.0 for further details.

Abbreviations used in this table appear on the final page of the table.

Table 4: Long-Term Follow-Up Schedule of Events (Contd)

Procedure[a]	Safety Follow-Up Visit 1[b]	Safety Follow-Up Visit 2[b]	Survival Follow-Up[c] Every 12 Weeks (± 14 Days)	Notes[d]
Brain Imaging	• Patients with a history of brain metastasis or neurological symptoms should have MRI with and without contrast. See Section 7.2 if patient has contraindications to contrast MRI. • Brain imaging assessments should be performed on same schedule as body tumor assessments, or as clinically indicated • Tumor assessments will continue until both BICR and Investigator's assessments of tumor images have determined progression. • Patients who are receiving study treatment beyond progression should continue scans until the criteria for treatment discontinuation are met and BICR-assessed progression has occurred. • Tumor assessments are no longer required if subsequent anticancer therapy is started, even if the patient has not yet progressed. • Use same imaging method as was used at screening.			All study treatment decisions will be based on the Investigator's assessment of tumor images. See Section 7.0 for further details.
Survival Status			X	Survival Follow-up can be administered in person or by telephone, if needed.
Health Outcomes Assessments				
EQ-5D-3L	X			See Section 7.6 for further details.
FKSI-19	X			
PRO-CTCAE	X			
Health Care Resource Utilization	X			Study site staff should collect health care resource utilization data using the CRF.

AE = adverse event; BICR = blinded independent central review; CT = computed tomography; CRF = case report form; CVA = cerebrovascular accident; ECG = electrocardiogram; eCRF = electronic case report form; EQ-5D-3L = 3-level version of the EuroQol Group's EQ-5D; FKSI-19 = Functional Assessment of Cancer Therapy (FACT) Symptom Index for Kidney Cancer; hCG = human chorionic gonadotropin; IMDC = International Metastatic RCC Database Consortium; IV = intravenous(ly); MRI = magnetic resonance imaging;

MUGA = multigated acquisition; PK = pharmacokinetic(s); PO = orally; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; q3w = every 3 weeks; RCC = renal cell carcinoma; SAE = serious adverse event; TIA = transient ischemic attack; UPCR = urine protein creatinine ratio; VW = vital signs and weight only; WOCBP = women of childbearing potential

a. Assessments and visits that occur outside of protocol-specified windows (e.g., for holidays, travel issues, insurance issues) may be acceptable on a case-by-case basis after review by the Medical Monitor.
b. Patients must be followed for 100 days after the last dose of study treatment. Safety Follow-Up Visit 1 should occur 30 (± 7) days from the last dose of all study drug(s), or at the time of permanent treatment discontinuation if discontinuation is after the Safety Follow-Up Visit 1 window. Safety Follow-Up Visit 2 occurs 100 (± 7) days from the last dose of all study drug(s). Safety Follow-up Visits should occur regardless of initiation of subsequent anticancer therapy. Both Safety Follow-up Visits should be conducted in person.
c. Survival Follow-Up to occur every 12 weeks (± 14 days) following the Safety Follow-Up Visit 2. Survival Follow-Up may be conducted in person or by telephone. The Sponsor may request that survival data be collected on all treated patients outside of the 3-month specified window. At the time of this request, each patient will be contacted to determine their survival status unless the patient has withdrawn consent for all contact. Information about subsequent anticancer therapy will also be collected during these contacts.
d. Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used for safety monitoring purposes by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

2.0 INTRODUCTION

This is a Phase 3, randomized, open-label study of bempegaldesleukin (NKTR-214) combined with nivolumab compared with the Investigator's choice of a tyrosine kinase inhibitor (TKI) therapy (either sunitinib or cabozantinib monotherapy) in previously untreated patients with advanced or metastatic renal cell carcinoma (advanced RCC).

The immunogenic properties of NKTR-214 in combination with checkpoint inhibitors that target and inhibit the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway make it a potentially promising combination therapy. The side effect profile of NKTR-214 does not overlap with that of checkpoint inhibitors, further supporting the use of NKTR-214 as a potentially complementary combination partner with checkpoint inhibitors.

This Phase 3 study will allow direct comparison of NKTR-214 combined with nivolumab versus TKI therapy of Investigator's choice (sunitinib or cabozantinib) as measured by overall survival (OS), objective response rate (ORR), and other clinical endpoints in treatment-naive patients with advanced RCC.

2.1 Study Rationale

In the Phase 1/2 setting, NKTR-214 combined with nivolumab has demonstrated encouraging clinical activity, as measured by ORR, in multiple tumor types including RCC. Given the durability of responses associated with immunotherapies, NKTR-214 combined with nivolumab is hypothesized to lead to greater clinical benefit, as measured by ORR, progression-free survival (PFS), or OS, compared to tyrosine kinase inhibitors of Investigator's choice (sunitinib or cabozantinib), a widely used standard-of-care agent in this patient population. This study will allow for direct comparison of ORR, PFS and OS between arms. If NKTR-214 combined with nivolumab has an acceptable safety profile and is shown to improve ORR or OS, versus the tyrosine kinase inhibitors, this study may support the approval of NKTR-214 combined with nivolumab in patients with previously untreated advanced RCC.

2.1.1 Research Hypothesis

Treatment with NKTR-214 combined with nivolumab will improve ORR and OS when compared to sunitinib monotherapy or cabozantinib monotherapy in patients with previously untreated advanced RCC.

2.2 Background

2.2.1 Renal Cell Carcinoma - Epidemiology

Renal cell carcinoma (RCC) is the eighth most common cancer in the world and is increasing in incidence (Znaor, 2015). Globally, RCC occurs in more than 330,000 cases with approximately a third of the patients succumbing to their disease. Despite the earlier detection of smaller kidney tumors, the rate of RCC-related mortality has increased, suggesting that recurrence and advanced disease are responsible for mortality (Sun, 2011; Hollingsworth, 2006). With the rise

in RCC incidence, as well as mortality and morbidity associated with advanced RCC, the medical need for improved treatment options in this population remains.

Multiple scoring systems are available to characterize prognosis in treatment-naive RCC. Two of the most commonly used are the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic scoring system and the International Metastatic RCC Database Consortium (IMDC) prognostic scoring system (see Appendix 1). Each of these systems categorizes patients as favorable-, intermediate-, or poor-risk based on how many adverse prognostic factors are present (0: favorable risk, 1-2: intermediate risk, 3 or more: poor risk). The six parameters of importance for IMDC prognostic score classification are Karnofsky Performance Status (Appendix 2), time from diagnosis to treatment, hemoglobin value, corrected calcium concentration, absolute neutrophil count, and platelet count. With each system, total number of adverse prognostic factors present has been shown to correlate with OS.

Approximately 25% of patients are in the favorable-risk group, 50% are in the intermediate-risk group, and 25% are in the poor-risk group. In an analysis of 1028 patients scored using the IMDC system, median OS for favorable-, intermediate-, and poor-risk patients was 43.2 months, 22.5 months, and 7.8 months, respectively (Heng, 2013).

2.2.2 Current Treatment

Until 2006 in the United States (US) and European Union (EU), the cytokines interleukin-2 (IL-2) and interferon-alpha (IFN-α) were the only active treatments for advanced RCC. Over the last several years, an increased understanding of the biology of RCC has led to development of multiple agents that target specific growth pathways. The vascular endothelial growth factor (VEGF) pathway and targeted serine/threonine protein kinase therapies that block the mammalian target of rapamycin (mTOR) have been found to be important targets in RCC disease. Global health authorities have approved multiple drugs targeting these pathways, including anti-VEGF agents, such as the tyrosine kinase inhibitors sunitinib, pazopanib, sorafenib, and cabozantinib, the anti-VEGF monoclonal antibody, bevacizumab, and mTOR pathway inhibitors, such as temsirolimus and everolimus (Banumathy, 2010).

In the Phase 2 CABOSUN study, cabozantinib showed superior PFS in the intermediate/poor risk population compared to sunitinib, which led to regulatory approval in first-line advanced RCC in United States for all risk types in 2017 (Choueiri, 2017). In 2018, cabozantinib also was approved for the treatment of first-line advanced RCC intermediate/poor risk population in the EU (Cabometyx, 2018). CABOSUN study was not powered to show benefit in OS, which remains to be demonstrated against sunitinib by another TKI. The ORR, PFS and OS data reported for sunitinib in favorable-risk patients had long been unchallenged and sunitinib remains a preferred standard of care in this population (Motzer, 2018a).

Recent innovation of treating cancer with immunotherapies has also expanded treatment options. Nivolumab, an anti-PD-1 antibody, given as monotherapy or in combination with the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, ipilimumab, has

demonstrated clinical activity in multiple tumor types, including RCC. Recently in the Phase 3 CA209214 study, nivolumab in combination with ipilimumab showed superior clinical efficacy, ORR and OS along with a positive trend in PFS compared to sunitinib in patients with previously untreated intermediate/poor risk advanced RCCs and is the new standard of care in this patient population (Motzer, 2018b). The nivolumab/ipilimumab combination received Food and Drug Administration (FDA) approval in the US in April 2018 and European Medicines Agency approval in the EU in November 2018; health authority submissions in other countries are underway. Most recently, the combination of pembrolizumab (an anti-PD-1 antibody) and another TKI, axitinib, demonstrated statistically significant OS and PFS improvement over sunitinib in all risk groups of patients with previously untreated advanced RCC (Rini, 2019), and the combination of avelumab (an anti-PD-L1 antibody) with axitinib also demonstrated statistically significant PFS improvement over sunitinib (Motzer, 2019). These data led to FDA approval of these combinations in the US in April 2019 and May 2019, respectively. Although combinations of more than one checkpoint inhibitor and combinations of checkpoint inhibitors with TKIs significantly improved clinical outcome, the potential for long-term disease control may be improved with combination immune-oncology agents. If tolerable toxicity, this may prove a preferred option in patients with first-line RCC.

According to the most recent National Comprehensive Cancer Network (NCCN) guidelines there are several recommended treatment options for first-line, advanced RCC (NCCN, 2019). These include TKIs (sunitinib, cabozantinib [intermediate- and poor-risk patients], pazopanib, axitinib, and temsirolimus [poor prognosis patients only]), nivolumab in combination with ipilimumab (intermediate- and poor-risk patients), and axitinib in combination with pembolizumab. High-dose IL-2 is also a choice for select patients. Given the global availability of sunitinib for this international clinical trial and the countries included in this trial, sunitinib was selected for the control arm of this trial. At the time of the trial conception, cabozantinib is available in the US and EU for intermediate- and poor-risk patients, having shown improved PFS in a randomized clinical trial involving 157 patients. Pazopanib (available in the US, EU, United Kingdom [UK], and Australia) did not show improved PFS or OS when compared to sunitinib (Motzer, 2013; Motzer, 2014). Given the complexity of global supply (to supply 3 versus 2 agents for the control arm) and the limited availability of pazopanib, a decision was made to prioritize the selection of sunitinib and cabozantinib, which remain among the preferred monotherapy TKI options in the targeted advanced RCC patient population.

2.2.3 NKTR-214 Mechanism of Action

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 (IV) 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 IL-2 mediated adverse events (AEs) 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 regulatory T cells (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 Tregs that are activated through the IL-2 receptor alpha beta gamma (IL-2Rαβγ) (Charych, 2016a; Charych, 2016b).

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 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 complementary combination partner with checkpoint inhibitors.

2.2.4 Study 15-214-01 (EXCEL; NKTR-214 Monotherapy)

The NKTR-214 clinical development program started with the monotherapy study EXCEL (Study 15-214-01; 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). The first part of the study was a dose escalation phase, designed to evaluate the safety and tolerability, and define the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of NKTR-214. The second part of the study was an expansion phase following identification of the RP2D, designed to evaluate the safety and tolerability, as well as the efficacy of NKTR-214 in specific tumor types. NKTR-214 at a dose of 0.009 mg/kg administered every 3 weeks (q3w) was deemed the MTD by pre-defined dose-limiting toxicity criteria. The RP2D was determined to be 0.006 mg/kg q3w. Enrollment was closed after 28 patients were exposed to NKTR-214 in the dose-escalation phase and the dose expansion phase was not initiated.

The safety of single-agent NKTR-214 has been assessed in 28 patients across 5 dose cohorts administered NKTR-214 q3w at doses ranging from 0.003 mg/kg to 0.012 mg/kg and a dosing frequency of every 2 weeks (q2w) was explored at 0.006 mg/kg. For the q3w dosing frequency, doses up to 0.009 mg/kg were well tolerated. One patient dosed at 0.012 mg/kg experienced

cytokine release syndrome (CRS) and the dose-limiting toxicities of hypotension and syncope; this patient received 2 additional cycles of NKTR-214 at a lower dose of 0.006 mg/kg.

As of the data cutoff date of 29 March 2018, 593 treatment-emergent AEs were reported among the 28 patients who received single-agent NKTR-214. Overall, the most common treatment-emergent AEs were fatigue (23 patients, 82.1%), flu-like symptoms (consisting of influenza-like illness, influenza, pyrexia, and chills; 20 patients, 71.4%), pruritus (19 patients, 67.9%), hypotension (18 patients, 64.3%), rash (consisting of erythema, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, rash generalized, and rash macular; 15 patients, 53.6%), decreased appetite (15 patients, 53.6%), and arthralgia or cough (12 patients, 42.9% each).

The most common AEs considered by the Investigator to be related to NKTR-214 were fatigue (20 patients, 71.4%), flu-like symptoms (19 patients, 67.9%), pruritus (18 patients, 64.3%), hypotension (16 patients, 57.1%), rash (14 patients, 50.0%), decreased appetite (13 patients, 46.4%), and arthralgia or cough (9 patients, 32.1% each). Such treatment-related AEs as flu-like symptoms, rash and pruritus were generally mild or moderate in severity, predictable, manageable, and short-lived. These IL-2 mediated AEs generally occurred 3 to 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 non-steroidal anti-inflammatory drugs (NSAIDs) and the cases of rash/pruritus were either self-limiting or treated with anti-histamines (steroids were administered for occasional patients who had severe rash/pruritus).

The most frequently reported Grade ≥ 3 events were hypotension (5 of 28 patients, 17.9%), syncope (3 patients, 10.7%), metastases to central nervous system (3 patients, 10.7%), and abdominal pain, headache (1 of 2 related), and anemia (each: 2 patients, 7.1%).

Six of 28 patients reported Grade 3 treatment-related AEs, which included hypotension, abdominal pain, infusion-related reaction, headache, and syncope. The cases of Grade 3 hypotension were rapidly reversed with intravenous fluids, and a hydration management guideline was implemented during the study which mitigated the hypotension severity. One patient, who had a prior history of an infusion reaction to a previously administered immunotherapy, discontinued treatment due to an infusion-related reaction following the first dose of NKTR-214. With the exception of one event of hypothyroidism, no other immune mediated AEs consistent with checkpoint inhibitors were reported. No patient experienced capillary leak syndrome and no Grade 4 treatment-related AEs or treatment-related deaths were reported on the study.

Fifteen patients (53.6%) reported 31 serious adverse events (SAEs) in monotherapy Study 15-214-01. Eleven SAEs reported among 7 (25.0%) patients were considered related to treatment. The only treatment-related SAE reported for more than 1 patient was hypotension (5 patients, 17.9%, 4 of 5 were Grade 3 in severity). While no objective responses were observed in Study 15-214-01, 9 patients experienced tumor shrinkage between 1% and 30% and two patients, after progressing on multiple prior therapies, had durable stable disease over 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 stable disease for 18 months. A second patient with metastatic RCC, who had progressed on high-dose IL-2 and was refractory to single-agent OX40 (i.e., an antibody targeting the tumor necrosis factor receptor superfamily member 4) and nivolumab, was treated with 19 cycles of NKTR-214 and had durable stable disease for 14 months. Given the biological properties of NKTR-214 and nivolumab these observations further supported the rationale for combining these two agents.

2.2.5 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses (Pardoll, 2003; Zitvogel, 2006; Dunn, 2002). Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR) (Greenwald, 2005). Collectively, these signals govern the balance between T-cell activation and tolerance. PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, inducible T-cell co-stimulator (ICOS), and B- and T-lymphocyte attenuator (BTLA) (Freeman, 2000). PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-gamma (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes (Sharpe, 2007). These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab

enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) (Wolchok, 2009).

2.3 Benefit/Risk Assessment

2.3.1 Nivolumab in Renal Cell Carcinoma

Nivolumab monotherapy has been studied in patients with advanced RCC in several Bristol-Meyers Squibb-sponsored studies (Phases 1 through 3): MDX1106-03, CA209009, CA209010, and CA209025. MDX1106-03 was a Phase 1 refractory solid tumor trial, which included 34 patients with previously treated advanced RCC who received nivolumab at 1 mg/kg (n = 18) or 10 mg/kg (n = 16) given every 2 weeks (McDermott, 2015; Motzer, 2015b; Topalian, 2012). Median PFS was 7.3 months. In both the 1 mg/kg and 10 mg/kg cohorts, approximately 30% of patients experienced an objective response with median duration of response of 12.9 months. Responses were generally rapid with a median time to response of 16 weeks. Notably, responses could occur after treatment cessation and persist off treatment. Median overall survival was 22.4 months. These results were promising given that many of the patients were heavily pre-treated with 71% having had 2 or more lines of therapy. Treatment-related AEs of any grade were observed in 85% of RCC patients, the most common being fatigue (41%), rash (27%), diarrhea (18%), and pruritus (18%). Grade 3-4 treatment-related AEs were observed in 18% of RCC patients. The spectrum, frequency, and severity of treatment-related AEs were similar in the RCC population compared to the overall study population and were similar across dose levels.

In order to identify a potential dose-response relationship in RCC, a randomized Phase 2 study (CA209010) was conducted in 168 patients with advanced RCC previously treated with an antiangiogenic therapy who received nivolumab at 0.3 mg (n = 60), 2 mg/kg (n = 24) or 10 mg/kg (n=54) given every 3 weeks (Robert, 2017). No dose response relationship was found as measured by PFS, with median PFS of 2.7, 4.0, and 4.2 months for the 0.3, 2, and 10 mg/kg groups, respectively (P = 0.9); ORR was 20%, 22%, and 20% in the 0.3, 2, and 10 mg/kg groups, respectively. Median time to achievement of an objective response was 2.8-3.0 months. The median duration of response was 22.3 months (4.8, not reached) in the 10 mg/kg arm and not yet reached in the 2 lower dose cohorts. Median OS was at 18.2 to 25.5 months, with a minimum of follow-up of 24 months. Fatigue was the most frequent toxicity (22-35%). No new toxicities were identified with 11% experiencing Grade 3-4 treatment-related AEs, none of which were due to pneumonitis. Treatment-related AEs led to discontinuation of study drug in 7% of patients

A parallel biomarker-focused trial, CA209009, using the same 3 nivolumab dose levels (0.3, 2, and 10 mg/kg every 3 weeks) was executed to explore predictors of response and identify mechanisms of resistance (Spigel, 2017). This study included 67 patients with previously-treated, advanced RCC who were randomized to one of the 3 nivolumab dose groups and 24 patients with previously-untreated RCC who received nivolumab at 10 mg/kg every 3 weeks. The results mirrored the efficacy and toxicity profile of CA209010 with an overall ORR of 18% in previously treated patients, and 13% in previously untreated patients and disease

stabilization in another 32% of previously treated and untreated patients. At 24 weeks, 36% of patients were free from progression. Of 56 patients with evaluable pretreatment tumor samples, 18 (32%) had ≥ 5% PD-L1 tumor expression. ORR was 22% among those with ≥ 5% PD-L1 tumor expression versus 8% among those with < 5% PD-L1 tumor expression.

Based on the clinical activity of nivolumab observed in these Phase 1 and 2 studies, a large Phase 3 trial (CA209025) was conducted in 821 patients with advanced RCC previously treated with 1 or 2 antiangiogenic therapies who were randomized to receive nivolumab 3 mg/kg every 2 weeks or everolimus 10 mg daily (Motzer, 2015a). A planned interim analysis, after a minimum of follow-up of 14 months, demonstrated a statistically significant and clinically meaningful improvement in OS of nivolumab monotherapy vs everolimus (median OS, 25.0 months vs 19.6 months, respectively; hazard ratio [HR] = 0.73 [98.5% CI, 0.57 to 0.93], p-value = 0.002). ORR was 25% for nivolumab vs 5% for everolimus. Among 756 patients with quantifiable PD-L1 tumor expression in pretreatment samples, 24% had 1% PD-L1 expression. Among patients with ≥1% PD-L1 expression, median OS was 21.8 months in the nivolumab group and 18.8 months in the everolimus group (HR, 0.79; 95% CI, 0.53 to 1.17). Among patients with <1% PD-L1 expression, the median OS was 27.4 months in the nivolumab group and 21.2 months in the everolimus group (HR, 0.77; 95% CI 0.60 to 0.97). No new safety concerns were identified, and nivolumab monotherapy showed a favorable safety profile as compared to everolimus, evidenced by the lower rates of drug-related AEs (all grades, 79% vs 88%; Grade 3-4, 19%-37%, respectively) and drug-related AEs leading to discontinuation (all grades, 8% vs 13%, respectively) in the nivolumab group. These results were the basis for regulatory approval of nivolumab monotherapy in advanced RCC.

Promising safety and efficacy results were also observed with the combination of nivolumab and ipilimumab in the advanced RCC population in Study CA209016 (Hammers, 2017), a Phase 1 dose-escalation study of nivolumab in combination with vascular endothelial growth factor receptor (VEGFR)-TKIs or ipilimumab in patients with advanced RCC. The dosing regimen including nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg (N3 + I1) was chosen for further clinical evaluation because it exhibited similar clinical activity to nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg (N1+ I3) but had a more favorable safety profile.

A Phase 3 trial CA209214 evaluated nivolumab combined with ipilimumab (N3+ I1 regimen) against sunitinib in first-line advanced RCC. Patients were stratified according to IMDC risk score and region (Motzer, 2018b). Nivolumab + ipilimumab combination therapy demonstrated statistically significant and superior OS compared with sunitinib monotherapy in the primary population which comprised intermediate- and poor-risk patients (HR: 0.63 [99.8% CI: 0.44, 0.89]; stratified log-rank test 2-sided p-value < 0.0001) at the adjusted alpha of 0.002. Median OS was not reached at the time of database lock for this report in the nivolumab + ipilimumab group and was 25.95 months in the sunitinib group. Nivolumab + ipilimumab combination therapy demonstrated a statistically significant higher ORR using an independent radiology review committee (41.6% [95% CI: 36.9, 46.5]) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) than sunitinib monotherapy (26.5% [95% CI: 22.4, 31.0])

p-value < 0.0001. 9.4% vs 1.2% of patients achieved a complete response (CR) in the nivolumab + ipilimumab and sunitinib groups, respectively. With a delayed separation of the PFS curves in Kaplan Meier analysis, the PFS HR was 0.82, [99.1% CI: 0.64-1.05], with stratified log-rank 2-sided p-value = 0.0331, which did not meet the pre-specified α boundary of 0.009 to achieve statistical significance although the difference in median survival was > 3 months.

Among 776 intermediate- and poor-risk patients who had quantifiable PD-L1 expression, 100 of 384 patients (26%) in the nivolumab-plus-ipilimumab group and 114 of 392 patients (29%) in the sunitinib group had 1% or greater PD-L1 expression. In exploratory analyses, overall survival among the 776 patients was longer with nivolumab plus ipilimumab than with sunitinib across PD-L1 expression levels. The 12-month overall survival rate with less than 1% PD-L1 expression was 80% (95% CI, 75 to 84) with nivolumab plus ipilimumab and 75% (95% CI, 70 to 80) with sunitinib, and the 18-month overall survival rate was 74% (95% CI, 69 to 79) and 64% (95% CI, 58 to 70), respectively; the median overall survival was not reached in both groups (hazard ratio for death, 0.73; 95% CI, 0.56 to 0.96). In patients with 1% or greater PD-L1 expression, the 12-month overall survival rate was 86% (95% CI, 77 to 91) with nivolumab plus ipilimumab and 66% (95% CI, 56 to 74) with sunitinib, and the 18-month overall survival rate was 81% (95% CI, 71 to 87) and 53% (95% CI, 43 to 62), respectively; the median overall survival was not reached and 19.6 months (95% CI, 14.8 to not estimable), respectively (hazard ratio for death, 0.45; 95% CI, 0.29 to 0.71).

The objective response rate among patients with less than 1% PD-L1 expression was 37% with nivolumab plus ipilimumab and 28% with sunitinib (P = 0.03); among patients with 1% or greater PD-L1 expression, the objective response rate was 58% versus 22% (P<0.001). The median PFS among patients with less than 1% PD-L1 expression was 11.0 months with nivolumab plus ipilimumab and 10.4 months with sunitinib (hazard ratio for disease progression or death, 1.00; 95% CI, 0.80 to 1.26); among patients with 1% or greater PD-L1 expression, the median PFS was 22.8 and 5.9 months, respectively (hazard ratio for disease progression or death, 0.46; 95% CI, 0.31 to 0.67). A similar trend was observed among patients with 5% or greater PD-L1 expression, as compared with patients with less than 5% PD-L1 expression.

2.3.2 Observed Events of Cerebrovascular Accident

2.3.2.1 Initial Analysis of Cerebrovascular Accident Events in Study 16-214-02 (PIVOT-02)

Serious events of cerebrovascular accident (CVA), including one fatal event, have been observed in patients who have received NKTR-214 in the triplet combination with nivolumab and ipilimumab, in the doublet combination with nivolumab, and in the combination of NKTR-214, nivolumab, and other anticancer therapy.

As of 28 October 2019, 3 of 43 patients (7.0%) who received triplet therapy in Study 16-214-02 (PIVOT-02) had CVA events, including one fatal event, all of which were considered by the Investigator to be related to treatment with NKTR-214, nivolumab, and ipilimumab. Additionally, 9 of 488 patients (1.8%) who received doublet therapy (NKTR-214 and

nivolumab) had 10 CVA events, which were considered by the Investigator to be related to at least one of the study treatments in 4 patients (3 related to the NKTR-214 and nivolumab-doublet therapy and 1 related to nivolumab monotherapy); and one of 10 (10.0%) patients who received combined NKTR-214, nivolumab, and other anticancer therapy (platinum-based chemotherapy) had a CVA event, which was considered by the Investigator to be unrelated to study treatment.

2.3.2.2 Updated Analysis of CVA Events Observed with NKTR-214

A cumulative search of the NKTR-214 global safety database was conducted on 28 October 2020, which included 1345 patients who received NKTR-214 in triplet combinations with nivolumab plus ipilimumab or with nivolumab plus NKTR-262 (a toll-like receptor agonist 7/8); in doublet combinations with checkpoint inhibitors; in a doublet combination (NKTR-214 with nivolumab) plus chemotherapy, and in combination with NKTR-262 from the following studies: 15-214-01, 16-214-02, 16-214-05, 17-214-09, 18-214-10, 20-214-29, CA045-001 (17-214-08), CA045-009 (18-214-03), CA043-010 (18-214-14), SP-IND, and 17-262-01.

Overall, 1.9% (26 of 1345) of patients exposed to NKTR-214 reported CVA events. Of the 26 patients, 13 patients experienced Grade 3 or 4 events and 4 patients had a fatal outcome. The mean time to first CVA event was 218.7 days (range 4 to 727 days; median 158 days). Twenty of the 26 patients with CVA events received a doublet combination with a checkpoint inhibitor, which included 1.7% (19 of 1116) of patients who received nivolumab, 1.3% (1 of 76) who received pembrolizumab, and 0% (0 of 23) who received atezolizumab.

Based on these events, CVA was escalated to an adverse event of special interest (AESI) in 2020 and mitigations were put in place to reduce the risk of CVA. These mitigations include implementation of a CVA adverse event management algorithm (Appendix 6) 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.

2.3.3 Mitigation Measures

Following the comprehensive review of the entire NKTR-214 clinical program, additional safety measures and analyses were implemented to mitigate the risk of CVA events and to expedite reporting of CVA events by identifying CVA as an AESI. These safety measures and analyses are reflected in changes to the following protocol sections: study exclusion criteria (Section 4.2), hydration guidelines (Sections 1.2 and 5.4.2.2), CVA AE management algorithm (Appendix 6), [redacted] for characterization of CVA events (Sections 1.2 and 5.10.3; Table 6; Appendix 6), criteria to delay, resume, or permanently discontinue study drug (Section 5.13), management algorithms for immune-mediated AEs (Section 5.13.8), anticoagulation (Section 5.15.3.3), prohibited medications (Section 5.15.3.1), and reporting AESIs (Section 8.11).

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

2.3.4 Nivolumab and NKTR-214 in Renal Cell Carcinoma

Preliminary data on the combination of nivolumab and NKTR-214 in 26 patients with previously untreated advanced RCC was recently presented (Diab, 2018a). Patients were administered nivolumab at a flat dose of 360 mg every 3 weeks, in combination with NKTR-214 at 0.006 mg/kg, both by intravenous infusion. Patients were evaluated using Fleming 2-stage design, in which efficacy was assessed by ORR (local Investigator) and subsequently confirmed by independent radiology review. A historical target ORR of 25% was set with a target ORR for the new combination of 50%. For the first stage, at least 6 out of 11 patients needed to demonstrate a confirmed ORR in order to reject the null hypothesis; at the final analysis, at least 10 out of 26 patients will be needed to reject the null hypothesis. Important baseline demographics included Eastern Cooperative Oncology Group (ECOG) performance status 0 (60%) or 1 (40%), and PD-L1 positive, negative, and unknown status at baseline equaled 29%, 63%, and 8%, respectively. In Stage 1, the target efficacy signal was met with 7 out of 11 patients with a response. Stage 2 with less mature data demonstrated 12 out of 26 patients with a response. Responses were observed in patients with both PD-L1 positive tumors (2 out of 7 patients; 29%) and negative tumors (9 out of 17 patients; 53%); 2 patients had unknown PD-L1 status. The trial is ongoing; the final analysis will be made at a future date.

2.3.5 NKTR-214 Safety Profile

NKTR-214 was designed to mitigate the severe toxicities associated with rapid systemic immune activation seen with administration of aldesleukin. The identified risks of NKTR-214 include hypotension, IL-2 mediated AEs (e.g., flu-like symptoms, rash, pruritus, fatigue, hepatic transaminase elevations, and serum creatinine elevations), infusion-related reactions/ hypersensitivity reactions, thyroid dysfunction, eosinophilia, and arthralgia. The majority of these AEs are mild to moderate in severity and can be monitored and managed in the clinical setting. The goal of engineering a PEGylated form of IL-2 that reduces the treatment-limiting toxicities of aldesleukin, that is, those necessitating in-hospital administration, appears to have been realized at the doses tested.

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

2.3.6 Nivolumab Safety Profile

Extensive details on the safety profile of nivolumab are available in the Investigator's Brochure and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy as well as in combination with ipilimumab is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with

relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed (see Section 5.13.8). Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab Investigator's Brochure.

2.3.7 NKTR-214 and Nivolumab Benefit and Risk Assessment

NKTR-214 has been generally well-tolerated in the clinical studies to date, both as monotherapy as well as in combination with nivolumab, with promising evidence of clinical efficacy and a potentially favorable benefit-risk profile. NKTR-214 has been safely administered in an outpatient setting supported by appropriate clinical monitoring.

Hypotension has been identified as a clinically significant adverse effect of NKTR-214 and can be effectively mitigated by prophylaxis and hydration guidelines. Other risks associated with NKTR-214 include IL-2 mediated AEs (e.g., flu-like symptoms, rash, pruritus, fatigue, hepatic transaminase elevations, and serum creatinine elevation), infusion-related reactions, thyroid dysfunction, eosinophilia, and arthralgia; these AEs are generally mild or moderate in severity and can be monitored and managed in the clinical setting. Cases of thyroid dysfunction (hypothyroidism, hyperthyroidism, thyroiditis), dermatitis, pneumonitis, hepatitis, myocarditis, myositis/myasthenia gravis, and vitiligo/hypopigmentation consistent with immune-mediated mechanism have been observed in patients receiving NKTR-214 plus nivolumab and some of these cases shared clinical characteristics consistent with immune-mediated AEs associated with checkpoint inhibitors.

The continued development of NKTR-214 in combination with nivolumab for the treatment of various cancers is warranted based on a positive benefit-risk profile. In addition, the early efficacy data along with the correlative biomarker showing conversion of PD-L1 negative tumors to PD-L1 positive tumors suggests that the addition of NKTR-214 to a checkpoint inhibitor (nivolumab) may change the tumor microenvironment in PD-L1 negative tumors such that the combination may contribute to anti-tumor activity invoke clinically significant, durable responses with an acceptable safety profile.

In conclusion, the currently available safety data demonstrates that NKTR-214 and nivolumab is a well-tolerated immuno-oncology combination therapy. Given the encouraging clinical activity and manageable and generally non-overlapping toxicity profile, the potential for direct benefit in patients warrants continued evaluation of the combination NKTR-214 and nivolumab in the clinical setting and supports further development of combination of NKTR-214 and nivolumab regimens in patients with cancer.

2.4 Scientific Rationale for Study Design

2.4.1 Sunitinib in Renal Cell Carcinoma

Sunitinib is a VEGF receptor TKI that is approved and recommended for the treatment of advanced RCC across prognostic groups (Escudier, 2012). In a randomized Phase 3 trial of sunitinib vs IFN-α in treatment-naive patients (including 36% with favorable risk, 57% with intermediate risk, and 7% with poor risk per MSKCC criteria), PFS (by independent radiology review) was significantly improved in the sunitinib group compared to the IFN-α group (median PFS 11 vs 5 months, HR = 0.42; p-value < 0.001). ORR was also greater in the sunitinib group (31% vs 6%). Median OS was 26.4 months in the sunitinib group vs 21.8 months in the IFN-α group (HR = 0.82; p-value = 0.051) (Motzer, 2009). More recently, sunitinib was compared to pazopanib in treatment-naive patients (including 27% favorable risk, 73% intermediate risk, and no poor risk) in the Phase 3 COMPARZ study (Motzer, 2013). In this non-inferiority study, sunitinib and pazopanib demonstrated similar median PFS (8.4 months for pazopanib vs 9.5 months for sunitinib, HR = 1.05) and median OS (28.4 months for pazopanib vs 29.3 months for sunitinib, HR = 0.91, p-value = 0.28). The ORR of pazopanib and sunitinib was 31% and 24%, respectively. The most common (≥ 20% frequency) adverse reactions include fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding (Sutent, 2019). Other important adverse reactions include hepatotoxicity, QT prolongation (including Torsades de Pointes), osteonecrosis of the jaw, tumor lysis syndrome, and thyroid dysfunction.

2.4.2 Cabozantinib in Renal Cell Carcinoma

Cabozantinib is a small molecule inhibitor of the tyrosine kinases c-Met, AXL, and VEGFR2, and has been shown to reduce tumor growth, metastasis, and angiogenesis. In vitro biochemical and/or cellular assays have shown that cabozantinib inhibits the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2 (Cabometyx, 2021). These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.

Cabozantinib has been evaluated in both first-line and second-line settings in advanced RCC. In patients with advanced RCC who progressed after previous VEGFR-TKI treatment, the randomized Phase 3 METEOR trial compared the efficacy and safety of cabozantinib monotherapy at a daily dose of 60 mg versus the mTOR inhibitor everolimus at a daily dose of 10 mg (Choueiri, 2015; Choueiri, 2016). In the trial, 658 patients were randomized to receive cabozantinib (n = 330) or everolimus (n = 328). After a minimum follow-up of 11 months in the first 375 randomized patients, the primary endpoint of PFS (by independent radiology review) was 7.4 months in the cabozantinib arm vs 3.8 months in the everolimus arm (HR = 0.58 [95% CI 0.45 to 0.75], p-value < 0.001). Using MSKCC criteria, subgroup analyses of risk groups

demonstrated PFS benefit in patients with favorable risk (HR = 0.54 [95% CI 0.37, 0.79]), intermediate risk (HR = 0.56 [95% CI 0.37, 0.84]), and poor risk (HR = 0.84 [95% CI 0.46, 1.53]). ORR was 17% in the cabozantinib arm vs 5% in the everolimus arm ($p < 0.001$). An interim OS analysis at the time of this final PFS analysis demonstrated a trend toward longer OS (HR = 0.67, p=0.005, with p-value ≤ 0.0019 required for statistical significance). A subsequent OS analysis, performed after a median follow-up of approximately 19 months in all 658 randomized patients, demonstrated a significant improvement in OS, with median OS of 21.4 months in the cabozantinib arm and 16.5 months in the everolimus arm (HR = 0.66 [95% CI 0.53-0.83]; p-value = 0.00026). Subgroup analyses of OS according to MSKCC risk group were consistent with the results for the overall population. The most common Grade 3 or 4 adverse events included hypertension (49 [15%] in the cabozantinib group vs 12 [4%] in the everolimus group), diarrhea (43 [13%] vs 7 [2%]), fatigue (36 [11%] vs 24 [7%]), palmar-plantar erythrodysesthesia syndrome (27 [8%] vs 3 [1%]), anemia (19 [6%] vs 53 [17%]), hyperglycemia (3 [1%] vs 16 [5%]), and hypomagnesemia (16 [5%] vs none). Serious adverse events Grade ≥ 3 occurred in 130 (39%) patients in the cabozantinib group and in 129 (40%) in the everolimus group. One treatment-related death occurred in the cabozantinib group (death; not otherwise specified) and two occurred in the everolimus group (1 aspergillus infection and 1 pneumonia aspiration).

In treatment-naive patients, cabozantinib was also evaluated in a randomized Phase 2 multicenter trial against sunitinib as first-line therapy in patients with advanced RCC (Choueiri, 2017). Patients were required to have either intermediate- or poor-risk disease according to IMDC criteria and were randomized in 1:1 ratio to cabozantinib (n = 79) or sunitinib (n = 78). Investigator-assessed PFS was the primary endpoint. Compared with sunitinib, cabozantinib treatment significantly increased median PFS (8.2 vs 5.6 months) and was associated with a 34% reduction in rate of progression or death (adjusted hazard ratio, 0.66; 95% CI, 0.46 to 0.95; one-sided p-value = 0.012). ORR was 46% (95% CI, 34 to 57) for cabozantinib vs 18% (95% CI, 10 to 28) for sunitinib. Median OS was 30.3 months for cabozantinib vs 21.8 months for sunitinib (adjusted HR = 0.80, 95% CI 0.50, 1.26). All-causality Grade 3 or 4 adverse events were 67% for cabozantinib and 68% for sunitinib and included diarrhea (cabozantinib, 10% vs sunitinib, 11%), fatigue (6% vs 15%), hypertension (28% vs 22%), palmar-plantar erythrodysesthesia (8% vs 4%), and hematologic adverse events (3% vs 22%). Treatment-related Grade 5 events occurred in 3 patients in the cabozantinib arm (acute kidney injury, sepsis, and jejunal perforation) and 3 patients in the sunitinib arm (sepsis, respiratory failure, and vascular disorders).

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

The ongoing PIVOT-02 study of nivolumab and NKTR-214 includes an expansion cohort in patients with treatment-naive advanced RCC. The most recent analysis is summarized in Section 2.3.3 (Diab, 2018a). Responses were observed in PD-L1 positive and negative patients. The combination of nivolumab with a safe and convenient delivery system of the CD122-biased

agonist (NKTR-214) may represent the highest possibility of cure and serve to fulfill unmet medical need.

2.4.4 Rationale for the Comparator

Tyrosine kinase inhibitors are one of the most commonly used first-line therapies for advanced RCC. Based on results of CABOSUN study (Section 2.2.2), cabozantinib has been approved as an accepted first standard-of-care regimen in both US and EU, in IMDC intermediate- and poor-risk patients. Sunitinib is listed by the NCCN guidelines as a preferred treatment and has been the comparator for most advanced RCC studies in the last several years. Although recent results from the CA209214, CABOSUN, and KEYNOTE-426 studies have shown superior efficacy of nivolumab + ipilimumab, cabozantinib, and pembrolizumab + axitinib, respectively, against sunitinib, patients benefit from individualized considerations for treatment options. Currently available combinations are associated with increased safety risks and/or rates of early discontinuation, and TKI monotherapy with either sunitinib or cabozantinib remains an acceptable option for patients with previously untreated advanced RCC. Inclusion of the most commonly used and preferred TKIs, sunitinib and cabozantinib, as choices in the control arm provide the Investigator with the ability to choose an appropriate TKI monotherapy option for their patients.

2.4.5 Rationale for Endpoints

The study will include primary endpoints of ORR and OS, to be evaluated in IMDC intermediate- or poor-risk patients and IMDC all-risk patients. Either OS or PFS, as long as there is no detriment in OS, have been successful endpoints to support drug approvals in advanced RCC. Sorafenib, sunitinib, bevacizumab, axitinib, everolimus and cabozantinib were each approved based on improvement in PFS. Based on improvement in OS, temsirolimus was approved for patients with untreated advanced RCC in a poor-risk population, the combination of nivolumab and ipilimumab in intermediate- and poor-risk patients, and most recently the combination of pembrolizumab and axitinib in patients with any IMDC risk score. Although tivozanib demonstrated a statistically significant improvement in PFS, this did not lead to regulatory approval, as a detriment in OS was noted in patients on the tivozanib arm. Objective response rate is included because of the improvement in ORR rates seen with the dual immunotherapy of ipilimumab combined with nivolumab in Studies CA209016 (Hammers, 2017) and CA209214 (Motzer, 2018b), with the intent to describe the ORR of NKTR-214 combined with nivolumab or TKI (sunitinib or cabozantinib) monotherapy. PFS was selected as a key secondary endpoint, but not as a primary endpoint as previous randomized trial in this population tend to show a late separation of the Kaplan Meier curves (nivolumab and ipilimumab versus sunitinib; Motzer, 2018b) or no separation (atezolizumab versus sunitinib; McDermott, 2018).

The evaluation of primary endpoints includes IMDC intermediate and poor-risk patients, which comprise approximately 75% of the total treatment-naive advanced RCC population. Inclusion of this large subset of patients in the primary endpoints of the study will allow for potential

meaningful differences in efficacy to be detected earlier than in the IMDC all-risk patient population. This may allow the NKTR-214 and nivolumab combination to become available to larger numbers of advanced RCC patients in a more timely fashion. Additional primary and key secondary endpoints include OS, ORR, and PFS in all IMDC risk (favorable, intermediate, and poor) patients. Promising response rates to the combination of NKTR-214 and nivolumab were observed among favorable-risk patients enrolled in the Phase 1/2 Study 16-214-02 (PIVOT-02), suggesting that the potential benefit of this combination may not be limited to intermediate- and poor-risk patients. Finally, one of the control arm agents, cabozantinib, is only approved for the treatment of intermediate- and poor-risk patients; whereas, the second control arm agent, sunitinib, is a preferred treatment option for favorable-risk patients and approved for use with all risks.

2.4.6 Rationale for Open-Label Design

The trial will have an open-label design with a blinded independent central review. Different dosing schedules and use of both IV infusions and oral medications across the 2 different arms make blinding the trial impractical. The complexity of including multiple visits for placebo infusions are burdensome for this patient population. Nivolumab is associated with some toxicities that are also common to cabozantinib and sunitinib (e.g., diarrhea, hepatotoxicity), and the management of these common toxicities are different for immuno-oncology agents (e.g., typically requiring steroids) vs TKIs (e.g., typically requiring dose delay and reductions). Therefore, an open-label trial is preferable for patient safety as it allows the optimal management of toxicities.

Due to the hydration program and the special restrictions for withholding anti-hypertensive medications in the NKTR-214 arm, a placebo-controlled, double-blinded design is not appropriate for this study.

2.4.7 Rationale for Stratification by IMDC Prognostic Score and TKI Choice

The IMDC prognostic score (Section 2.2.1) is known to have a profound effect on patient prognosis in terms of survival in advanced RCC, and the effectiveness of some treatment options in previously untreated advanced RCC is dependent on the different risk groups (Heng, 2013; Motzer, 2018b). It was also considered important to stratify patients based on TKI used in case there are differences in outcomes based on TKI choice.

2.4.8 Duration of Treatment for NKTR-214 Combined with Nivolumab

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumor types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of

patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment (Schadendorf, 2016).

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 patients with non-small cell lung cancer [NSCLC]), specified a maximum treatment duration of 2 years. Among 16 patients with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 patients were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years (Brahmer, 2017). These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2-year OS rates of 23% and 29%, and 3-year OS rates of 16%-18% for squamous and nonsquamous NSCLC respectively) (Felip, 2017).

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized Phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in patients with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR = 0.72, p-value = 0.00017) and pembrolizumab 10 mg/kg (HR = 0.60, p-value < 0.00001) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years (Herbst, 2016).

Keynote-006 was a randomized Phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2-year duration of pembrolizumab treatment. 104 (19%) of 556 patients randomized to pembrolizumab completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients (Robert, 2017).

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median

PFS (post-randomization) not reached vs 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (i.e., 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years (Spigel, 2017).

Collectively, these data suggest that there is minimal if any benefit derived from continuing immune-oncology treatment beyond 2 years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from Cycle 1 Day 1 (Arm A only).

Given the hypothesis that co-administration of NKTR-214 with nivolumab will potentiate the pharmacological effects of nivolumab, the duration of NKTR-214 therapy will also be restricted to 2 years from Cycle 1 Day 1 (Arm A only) to match the duration of nivolumab therapy.

2.5 Justification for Dose

2.5.1 Justification for Dose of NKTR-214

The dose for NKTR-214 is 0.006 mg/kg q3w taking in consideration the clinical safety profile associated with the robust immune system activation observed in the PIVOT-02 study. Refer to Section 2.3.2 for additional details on PIVOT-02.

2.5.2 Justification for Dose of Nivolumab

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, classical Hodgkin's lymphoma, head and neck, and urothelial carcinoma, using body weight normalized dosing (mg/kg), and has been safely administered at doses up to 10 mg/kg q2w. Nivolumab is currently approved for the treatment of various tumors, including melanoma, NSCLC, RCC, classical Hodgkin's lymphoma, squamous cell carcinoma of the head and neck, and urothelial carcinoma, using a regimen of either nivolumab 240 mg q2w or nivolumab 3 mg/kg q2w and nivolumab 480 mg every 4 weeks (q4w).

Nivolumab has been shown to be safe and well tolerated up to a dose level of nivolumab 10 mg/kg q2w. Population pharmacokinetic (PPK) analyses have shown that the pharmacokinetics (PK) of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including nivolumab 360 mg q3w. The simulated steady state average concentration (C_{avgss}) following administration of nivolumab 360 mg q3w are expected to be similar to those following administration of nivolumab 240 mg q2w and nivolumab 3 mg/kg q2w administered to patients weighing 80 kg, the approximate median weight of patients with NSCLC, melanoma and RCC used in the PPK analyses. Given that the

C_{avgss} estimates for nivolumab 360 mg q3w are predicted to be similar to those for nivolumab 240 mg q2w and nivolumab 3 mg/kg q2w, the efficacy is predicted to be similar for these regimens. It should be noted that the steady state peak concentrations following nivolumab 360 mg q3w are predicted to be less than those following the administration of nivolumab 10 mg/kg q2w providing sufficient safety margins. Further details on nivolumab 360 mg q3w dosing can be found in the Investigator's Brochure.

Finally, nivolumab 360 mg q3w is currently being investigated in combination with a number of other agents, including NKTR-214 in the PIVOT-02 study, and platinum-doublet chemotherapy dosing, with no new or increased safety events observed to date. By using nivolumab 360 mg q3w in this study, it allows for aligning doses of nivolumab at the same dosing frequency of the experimental agent.

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

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objectives are:

- To compare the ORR by blinded independent central review (BICR) assessment using modified Response Evaluation Criteria in Solid Tumors (mRECIST) 1.1 of NKTR-214 combined with nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC intermediate- or poor-risk patients with previously untreated advanced RCC
- To compare the ORR by BICR using mRECIST 1.1 of NKTR-214 combined with nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC all-risk patients with previously untreated advanced RCC
- To compare the OS of NKTR-214 combined with nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC intermediate- or poor-risk patients with previously untreated advanced RCC
- To compare the OS of NKTR-214 combined with nivolumab to that of TKI monotherapy (sunitinib or cabozantinib) in IMDC all-risk patients with previously untreated advanced RCC

3.2 Secondary Objectives

The key secondary objectives are:

- To compare the PFS by BICR using mRECIST 1.1 of NKTR-214 combined with nivolumab to TKI monotherapy (sunitinib or cabozantinib) in IMDC intermediate- or poor-risk patients with previously untreated advanced RCC
- To compare the PFS by BICR using mRECIST 1.1 of NKTR-214 combined with nivolumab to TKI monotherapy (sunitinib or cabozantinib) in IMDC all-risk patients with previously untreated advanced RCC

The other secondary objectives are:

- To estimate the incidence of AEs of NKTR-214 combined with nivolumab versus TKI monotherapy (sunitinib or cabozantinib) in patients with previously untreated advanced RCC
- To evaluate whether PD-L1 expression on tumor cells (< 1% vs ≥ 1%) using the PD-L1 immunohistochemistry (IHC) 28-8 pharmDx assay is a predictive biomarker for ORR, PFS, and OS in patients with previously untreated advanced RCC
- To characterize changes in cancer-related symptoms and quality-of-life in patients with previously untreated advanced RCC using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy (NCCN/FACT) Symptom Index for Kidney Cancer (FKSI-19)

[redacted]

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

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

1. Provide written, informed consent to participate in the study and follow the study procedures. The Investigator takes responsibility for ensuring that all vulnerable patients are protected and participate voluntarily in an environment free from coercion or undue influence.
2. Male or female patients, age 18 years or older at the time of signing the informed consent form (ICF)
3. Karnofsky Performance Status of at least 70% (see Appendix 2)
4. Measurable disease per mRECIST 1.1 criteria (by local Investigator; See Appendix 9)
5. Renal cell carcinoma diagnosis:
   a. Histological confirmation of RCC with a clear-cell component (tumors may also have sarcomatoid features), AND,
   b. Advanced (not amenable to curative surgery or radiation therapy) or metastatic (American Joint Committee on Cancer [AJCC] Stage IV) RCC
6. No prior systemic therapy (including neoadjuvant, adjuvant, or vaccine therapy) for RCC
7. Prior palliative radiotherapy must be completed at least 2 weeks prior to randomization. Patients must have recovered from all Grade 2 or higher radiation-related toxicities and not require corticosteroids.

   Note: Radiated lesions cannot be used as measurable lesions unless there is clear evidence of progression.

8. Patients are included with any IMDC score, whether favorable, intermediate, or poor risk. For IMDC ***intermediate- or poor-risk patients***, at least one of the following prognostic factors must be present (based on central laboratory results; see Appendix 1; See Section 8.15 for exceptions):
   a. Karnofsky performance status equal to 70%
   b. Less than 1 year from initial diagnosis (including original localized disease, if applicable) to randomization
   c. Hemoglobin < lower limit of normal

d. Corrected calcium > upper limit of normal (ULN):
corrected calcium = measured total calcium (mg/dL) + 0.8 (4.0 – serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL or
measured total calcium (mmol/L) + 0.02 (40 – serum albumin [g/L]), where 40 represents the average albumin level in g/L

e. Absolute neutrophil count > ULN

f. Platelet count > ULN

9. Demonstrated adequate organ function, as defined below, within 14 days of randomization:

a. Absolute neutrophil count (ANC) ≥ 1500/μL (≥ 1000/μL for patients with known or suspected diagnosis of benign ethnic neutropenia) after at least 14 days without growth factor support

b. Platelet count ≥ 100×10^3/μL after at least 14 days without transfusion

c. Hemoglobin ≥ 9.0 g/dL after at least 14 days without transfusion or growth factor support

d. Serum creatinine ≤ 1.5 × ULN (or estimated creatinine clearance ≥ 40 mL/min)

e. Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤ 3 × ULN

f. Total bilirubin ≤ 1.5 × ULN (total bilirubin ≤ 2 × ULN if associated with hepatobiliary metastases or Gilbert's syndrome)

g. Urine protein creatinine ratio (UPCR) < 1.0 (< 113 mg/mmol) or 24-hour urine protein < 1 gram (g)

Note: Patients with severe hepatic impairment (Child-Pugh Class C) are ineligible.

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

11. Oxygen saturation ≥ 92% on room air

12. Clinically significant toxic effect(s) of any prior anticancer therapy (if applicable) must be Grade 1 or resolved (except alopecia and sensory neuropathy). If the patient received major surgery, they must have complete wound healing and recovered from any complication from the surgery.

13. Reproductive Status

a. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within the 28 days prior to randomization

b. Women must not be breastfeeding

c. Women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of study treatment and for 5 months post treatment completion. Women should use an adequate method(s) of contraception as indicated in Appendix 4.

d. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of study treatment and 3 months post NKTR-214 completion. In addition, male patients must refrain from sperm donation during this time.

Investigators shall counsel WOCBP, and male patients who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4), which have a failure rate of < 1% when used consistently and correctly.

14. Patients must not have active brain metastases or any leptomeningeal metastases:

    a. Patients with brain metastases are eligible if these have been treated and there is no radiographic evidence of progression for at least 4 weeks after treatment is complete (confirmed by the head imaging obtained within 28 days prior to randomization). There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents; see Appendix 5 for corticosteroid dose equivalents) for at least 2 weeks prior to randomization. Stable dose of anticonvulsants is required at least 14 days prior to randomization. Treatment for central nervous system (CNS) metastases may include stereotactic radiosurgery (e.g., GammaKnife, CyberKnife, or equivalent) or neurosurgical resection. Patients who received whole brain radiation therapy are not eligible.

    b. No stereotactic radiation or craniotomy within 28 days of randomization

    c. No clinically significant symptoms secondary to brain metastases

    d. Head imaging must occur on study in accordance with Section 5.8

15. Archival or fresh tumor tissue, from a site not previously irradiated and with no intervening treatment between time of acquisition and randomization, identified and available to be provided as either a formalin-fixed, paraffin-embedded tissue block or unstained slides sectioned from a block within 3 months prior to randomization.

16. Patients must be able to swallow pills intact.

17. Patients must be able and willing to comply with the study visit schedule and study procedures.

4.2 Exclusion Criteria

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

1. Use of an investigational agent or an investigational device within 28 days of randomization
2. Female patients who are pregnant or lactating, who plan to get pregnant, or who have a positive serum or urine pregnancy test
3. Active, known, or suspected autoimmune disease that has required systemic treatment within the past 3 months; a documented history of clinically severe autoimmune disease that requires systemic steroids or immunosuppressive agents. (Exceptions include any patient on ≤ 10 mg/day of prednisone or equivalent, patients with vitiligo, hypothyroidism stable on hormone replacement, Type I diabetes, Graves' disease, Hashimoto's disease, alopecia areata, or eczema.)
4. History of allergy to study drug components (for nivolumab, NKTR-214, sunitinib and cabozantinib); for cabozantinib, this includes galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
5. History of severe hypersensitivity reaction to any monoclonal antibody
6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer. Prostate cancer is acceptable, provided that the following criterion is met: Stage T2N0M0 or lower.
7. History of organ or tissue transplant that requires systemic use of immune suppressive agents
8. Prior major surgery within 28 days of randomization ("major surgery" does not include biopsy or placement of a venous access device).
9. Any tumor invading the wall of a major blood vessel. Tumor extension into the lumen of the renal vein or vena cava without evidence of breaching the vessel wall (by computed tomography [CT] or magnetic resonance imaging [MRI]) is not considered invasion.
10. Any tumor invading the gastrointestinal (GI) tract or any evidence of endotracheal or endobronchial tumor within 28 days prior to randomization
11. Active infection requiring systemic therapy within 14 days prior to randomization (exception: Prophylactic use of antibiotics for signs of potential asymptomatic urinary tract infection or treatment of uncomplicated urinary tract infection with antibiotics is permitted)
12. Has known hepatitis B virus infection (e.g., hepatitis B surface antigen [HBsAg] reactive) or hepatitis C virus (HCV) infection (e.g., HCV ribonucleic acid [RNA] qualitative is detected)

13. Has known immunodeficiency or active human immunodeficiency virus (HIV-1/2 antibodies)
14. Prolonged Fridericia's corrected QT interval (QTcF) > 450 ms for men and > 470 ms for women at Screening
15. Known cardiovascular history including unstable or deteriorating cardiac disease within the previous 12 months prior to screening including but not limited to the following:
    a. Unstable angina or myocardial infarction
    b. Transient ischemic attack (TIA)/Cerebrovascular accident (CVA)
    c. Congestive heart failure (CHF) (New York Heart Association [NYHA] Class III or IV)
    d. Uncontrolled clinically significant arrhythmias
16. Need for > 2 antihypertensive medications for management of hypertension (including diuretics). Patients with hypertension must be on a stable anti-hypertensive regimen for the 14 days prior to randomization. Note: An antihypertensive medication that contains 2 drugs under one formulation is counted as 2 antihypertensive medications (e.g., angiotensin-converting-enzyme [ACE] inhibitor plus diuretic, calcium channel blocker plus ACE inhibitor).
17. History of pulmonary embolism (PE), deep vein thrombosis (DVT) (not including primary renal tumor thrombus), or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event (e.g., internal jugular vein thrombosis) within 3 months prior to randomization.
    a. Patients with a history of a venous or arterial thromboembolic event must be asymptomatic for at least 2 weeks prior to randomization and must be receiving a stable regimen of therapeutic anticoagulation (preferably low molecular weight heparin [LMWH] or direct oral anticoagulation [DOAC]; see Section 5.15.3.3 for further guidance). Note: unless there is a new medical contraindication observed after Cycle 1 Day 1, a patient with a history of venous or arterial thromboembolic event must be willing to maintain therapeutic anticoagulation throughout participation on the treatment phase of the study.
18. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to randomization
19. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of sunitinib or cabozantinib (e.g., malabsorptive disorder, ulcerative disease, uncontrolled nausea, vomiting, diarrhea, or small bowel resection)
20. Serious, non-healing wound or ulcer
21. Medically significant hemorrhage within 30 days of randomization; patients who are at risk of severe hemorrhage.

22. Patients who have received a live / attenuated vaccine within 30 days of randomization
23. Known current drug or alcohol abuse
24. Any contraindication or exclusions specific to sunitinib and cabozantinib included in the current Package Insert, Summary of Product Characteristics (SmPC), or the prescribing guidelines applicable to your country.
25. Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results (e.g., a condition associated with diarrhea or acute diverticulitis).
26. Patients with inadequately treated adrenal insufficiency

5.0 INVESTIGATIONAL PLAN

5.1 Study Design

This is a multicenter, randomized, open label, Phase 3 study that will evaluate the efficacy and safety of NKTR-214 combined with nivolumab compared with the Investigator's choice of a TKI, either sunitinib or cabozantinib, in patients with previously untreated advanced RCC.

The treatment period of the study is divided into multiple treatment cycles with associated evaluations and procedures. One cycle of treatment is defined as 6 weeks. Results of the assessments must be reviewed and documented before administering the scheduled dose of study drugs. In certain circumstances, patients with progressive disease (PD) per mRECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator; see Section 5.4.4 for treatment beyond progression criteria. This study is divided into a Screening period, a Treatment period, and a Long-Term Follow-Up period, which will continue until withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor.

Approximately 600 patients with previously untreated advanced RCC will be randomized in a 1:1 ratio between the two treatment arms:

- Arm A: NKTR-214 0.006 mg/kg IV q3w combined with nivolumab 360 mg IV q3w
- Arm B: The Investigator's choice of either one of the following treatments
  - Sunitinib 50 mg orally (po) once daily for 4 weeks followed by 2 weeks off

    OR
  - Cabozantinib 60 mg po once daily

Randomization will be stratified by:

- The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic score (0 [favorable risk] versus 1-2 [intermediate risk] versus 3-6 [poor risk]); laboratory data to calculate IMDC score are based on central laboratory results;
- TKI choice (sunitinib or cabozantinib)

Figure 1 provides the study schematic and the study procedures are provided in the Schedules of Events as follows:

- Screening Schedule of Events: Table 1
- On-Treatment Schedule of Events for Arm A: Table 2
- On-Treatment Schedule of Events for Arm B: Table 3
- Long-Term Follow-Up: Table 4

5.2 Screening Period

Patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. After signing the ICF, patients will be evaluated for entry criteria during the Screening period based on assessments outlined in Table 1. Rescreening after screen failure will be allowed.

5.3 Screening Failure

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities.

Patient re-screening: this study permits the re-enrollment of a patient that has discontinued the study as a pre-treatment failure (i.e., patient has not been randomized / has not been treated). If re-enrolled, the patient must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the patient's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 1 may be repeated in an effort to find all possible well-qualified patients.

5.4 Treatment Period

Patients will be treated until a maximum of 2 years from Cycle 1 Day 1 (Arm A only), disease progression per mRECIST 1.1 in the absence of clinical benefit as determined by the Investigator, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the patient decides to discontinue treatment or withdraw consent, the patient is lost to follow-up, or termination of the study by the Sponsor.

Patients with PD per mRECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator; see Section 5.4.4 for treatment beyond progression. Patients with a partial response (PR) or with stable disease (SD) will continue to receive study drugs until disease progression, or intolerability to therapy. It is at the discretion of the Investigator to continue treating patients with a confirmed CR, for a maximum treatment of 2 years from Cycle 1 Day 1 (Arm A only).

5.4.1 Administration of Study Drug

Patients should begin study treatment within 5 calendar days following randomization.

Table 5 provides the timing of study drug administration.

Table 5: Selection and Timing of Dose

Study Treatment	Starting dose	Frequency of Administration	Route of Administration
NKTR-214 [a]	0.006 mg/kg	Q3W	IV
Nivolumab	360 mg	Q3W	IV
Sunitinib	50 mg	A 6-week cycle, consisting of once daily regimen for 4 weeks followed by no treatment for 2 weeks	PO (with or without food)
Cabozantinib	60 mg (40 mg for patients with moderate hepatic impairment [Child-Pugh Class B])	once daily	PO (Food fasting is recommended 2 h prior and 1 h after administration)

a. NKTR-214 dose is based on IL-2 content

Child-Pugh Class is assessed using total bilirubin, serum albumin, prothrombin time, ascites and hepatic encephalopathy (for scoring, see Renown, 2018). Patients with mild hepatic impairment (Child-Pugh Class A) do not require a reduced starting dose of cabozantinib.

Patients randomized to Arm B must agree to complete a pill diary to record oral dosing, which will be reviewed by the Investigator or designee at the beginning of each cycle, starting with Cycle 2.

5.4.1.1 NKTR-214 Dosing

Each patient's NKTR-214 dose will be determined by the patient's weight in kilograms, which will be determined on the day of each NKTR-214 dosing. If the patient's weight is within 10% of the Cycle 1 Day 1 weight, the study drug doses do not need to be recalculated depending on institutional guidelines/preference. If the patient's weight has changed more than 10% from the Cycle 1 Day 1 weight, the dose of NKTR-214 must be recalculated and subsequent weight measurements should be compared with this new baseline weight to determine if further NKTR-214 dose recalculations are necessary.

Patients should receive NKTR-214 at a starting dose of 0.006 mg/kg on Day 1 and Day 22 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years (Arm A only) of treatment from Cycle 1 Day 1, the study ends, or other protocol-specified reasons in Section 5.4.3, whichever occurs first. Patients may be dosed no

less than 18 days from the previous dose. Study agent(s) should be administered in an area with access to resuscitation equipment.

NKTR-214 will be administered first, before nivolumab. NKTR-214 will be administered IV over 30 (± 5) minutes at a starting dose of 0.006 mg/kg every 3 weeks. The duration of infusion of NKTR-214 may be increased if necessary (e.g., patient history of infusion reaction) (see Pharmacy Manual for details).

Patients should be carefully monitored for infusion reactions during NKTR-214 administration. If an acute infusion reaction is noted, patients should be managed according to Section 5.13.9.

NKTR-214 treatment can continue for patients randomized to Arm A in the event that nivolumab is stopped due to toxicities.

[redacted]

Please refer to the Pharmacy Manual/current Investigator's Brochure for details regarding NKTR-214 reconstitution, preparation, storage, and administration.

5.4.1.2 Nivolumab Dosing

Nivolumab administration should start at least 30 minutes after the end of the NKTR-214 administration. Nivolumab will be administered IV over 30 (± 5) minutes at a dose of 360 mg. The duration of infusion of nivolumab may be increased if necessary (e.g., patient history of infusion reaction) (see Pharmacy Manual for details).

There will be no dose escalations or reductions of nivolumab allowed. Patients may be dosed no less than 18 days from the previous dose. Premedications are not recommended for the first dose of nivolumab.

Patients should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, patients should be managed according to Section 5.13.9.

[redacted]

[redacted]

[redacted]

Instructions for dilution and infusion of nivolumab injection will be provided in the Pharmacy Manual.

5.4.1.3 Sunitinib and Cabozantinib Dosing

Sunitinib will be administered on a 6-week cycle, starting at a dose of 50 mg once daily for 4 weeks, followed by 2 weeks of no treatment. Cabozantinib will be administered at a starting dose of 60 mg once daily; for patients with moderate hepatic impairment (Child Pugh Class B) the starting dose of cabozantinib will be 40 mg once daily. Food fasting is recommended for 2 hours before and 1 hour after cabozantinib administration. Table 7 provides the permitted doses for sunitinib and cabozantinib. Refer to the sunitinib (Sutent®) and cabozantinib (Cabometyx®) US Prescribing Information and/or the corresponding SmPC for updated dosing guidance or further information.

5.4.2 Monitoring Vital Signs and Hydration Guidelines

The study site must be equipped for medical emergencies.

5.4.2.1 Frequent Vital Signs

Refer to Section 8.17 for vital sign measurements, which are to be monitored according to the Schedule of Events (Section 1.2).

5.4.2.2 Hydration Guidelines for Arm A

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

electronic data capture (EDC). Oral hydration details during Cycle 1 will be captured in a patient hydration diary.

Adequate hydration mitigates the development of hypotension associated with NKTR-214 administration. Hydration and renal function must be assessed within 24 hours, or as soon as locally feasible, prior to NKTR-214 study drug administration see Appendix 3 for the list of analytes that require collection and evaluation prior to NKTR-214 study drug administration). For patients who must delay study treatment due to creatinine increase, see additional information regarding criteria to delay (Sections 5.13.1 and 5.13.2), resume (Section 5.13.7), or permanently discontinue study treatment (Section 5.14). Underlying reasons for decreased oral intake (e.g., nausea) should be addressed and treatment (e.g., IV hydration) should be provided. The Investigator may modify these recommendations based on the needs of the individual patient. Patients will also be provided a handout with hydration guidance.

Patients randomized to Arm A should be administered 1 liter of IV fluid on the day of each dosing of NKTR-214. Patients are to be instructed that for the next 3 days after administration of NKTR-214, they should drink at least 2 liters per day of self-administered oral hydration. Avoid activity that may contribute to dehydration (including, but not limited to, strenuous activity, long hot showers, and saunas) on the day of NKTR-214 administration and for the next 3 days after NKTR-214 administration.

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 (e.g., 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 (See Section 5.13.5).

Between 2 and 4 days, inclusive, following administration of the first 2 doses of 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 compliance and symptoms from the discussion (Section 1.2). Following subsequent NKTR-214 administrations, the oral hydration follow-up should be conducted as clinically indicated for patients receiving NKTR-214.

5.4.3 Duration of Treatment

Patients will remain on treatment until:

- Disease progression in the absence of clinical benefit as determined by the Investigator
- Death
- Unacceptable toxicity

- Symptomatic deterioration
- 2 years from Cycle 1 Day 1 (Arm A only)
- Investigator's decision to discontinue treatment
- Patient decision to discontinue treatment
- Patient withdraws consent
- Patient is lost to follow-up
- The Sponsor decides to terminate the study

5.4.4 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 (Wolchock, 2009; Nishino, 2015). Study treatment decisions will be based on the Investigator's assessment of tumor images and not on the BICR assessment (Section 7.4). Patients in both treatment arms will be permitted to continue on treatment beyond initial mRECIST 1.1-defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Patient tolerates study drug(s)
- Patient has stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., central nervous system metastases requiring immediate treatment).
- Patient provides written informed consent prior to receiving additional study treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

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

For patients who stay on treatment beyond mRECIST 1.1-defined PD, all study procedures (Section 1.2) should be performed continuously, including radiographic assessment by CT (preferred) or MRI on the described schedule in Section 7.0. CT/MRI assessments should continue until criteria for treatment discontinuation are met and BICR-assessed progression has

occurred. Tumor assessments are no longer required if subsequent anticancer therapy is started, even if the patient has not yet progressed.

Treatment beyond progression should be stopped when Investigator assesses a loss of clinical benefit. The criteria may include clinical disease progression, second PD of target lesions per mRECIST 1.1, radiographic progression of non-target lesions, or new lesions. Discussion with the Medical Monitor is encouraged.

5.5 Discontinuation from Study Treatment

Patients may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment. Patients may discontinue treatment of all or one of the study drugs based on AEs (see Section 5.13).

Reasons for discontinuation of study treatment are listed in Section 5.14.

In the event of a patient's withdrawal, the Investigator will promptly notify the Sponsor and make every effort to complete the Long-Term Follow-Up Schedule of Events specified in Table 4 (Section 1.2).

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

5.6 Long-Term Follow-Up

Long-term follow-up comprises 2 Safety Follow-Up Visits and Survival Follow-Up. For patients who discontinue study treatment, radiographic tumor assessments will continue to be collected every 9 weeks (± 7 days) from randomization through (and inclusive of) Week 54 and then every 12 weeks (± 7 days) until both BICR and Investigator's assessments of tumor images have determined progression, patient withdraws consent, patient begins a subsequent anticancer therapy, loss to follow up, death, or study termination by the Sponsor. Additional assessments are described in Table 4.

5.6.1 Safety Follow Up

- Safety Follow-up Visit 1 should occur 30 (± 7) days from the last dose of all study drug, or at the time of permanent treatment discontinuation if discontinuation is after the Safety Follow Up Visit 1 window.
- Safety Follow-up Visit 2 occurs 100 (± 7) days from the last dose of all study drug. Safety follow-up visits should occur regardless of initiation of subsequent anticancer therapy.
- Both Safety Follow-Up Visits should be conducted in person.
- Per clinical judgment, the patient may come in earlier for additional follow up.

- Patients will also be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drugs (NKTR-214 and/or nivolumab or TKI) as outlined in Sections 8.5 and 8.8.
- For AE and SAE reporting periods, please refer to Sections 8.5 and 8.7.

5.6.2 Survival Follow Up

- All patients will be contacted for survival every 12 weeks (± 14 days) following the Safety Follow-Up Visit 2 (or following last contact with the patient if Safety Follow-Up Visit 2 is missed).
- Survival visits may be conducted in person or by telephone.
- Information about subsequent anticancer therapy will also be collected during these contacts.
- The Sponsor may request that survival data be collected on all treated patients outside of the scheduled contacts. At the time of this request, each patient will be contacted to determine their survival status unless the patient has withdrawn consent for all contact or is lost to follow-up. Patients are not considered lost to follow up until after demonstration of due diligence with follow-up efforts. Alternative methods to determine survival status may be used (e.g., access to medical records and public record searches) as allowed by local regulations and/or guidelines.
- For patients who discontinue study treatment, radiographic tumor assessments will continue to be collected every 9 weeks (± 7 days) from randomization through (and inclusive of) Week 54 and then every 12 weeks (± 7 days) until both BICR and Investigator's assessments of tumor images have determined progression, patient withdraws consent, death, initiation of subsequent anticancer therapy, loss to follow up, or study termination by the Sponsor.
- Additional subsequent anticancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after next line of therapy will be collected.
- Survival follow up should continue until patient withdrawal of consent for survival follow up, death, loss to follow-up, or study termination by the Sponsor.

5.7 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.

5.8 Tumor and Radiographic Assessments

Tumor assessments for all patients will be performed as specified in Section 1.2.

Tumor response will be evaluated using mRECIST 1.1 described in Section 7.0.

Radiographic assessments (chest/abdomen/pelvis) are required for all patients for tumor measurements. MRI of the brain without and with contrast is required for patients at baseline. CT of the brain (without and with contrast) can be performed if MRI is contraindicated.

Documented tumor measurements are required using CT scans, MRI, physical examination, and/or digital photography, as appropriate. Any imaging used to assess disease at any time point will be submitted for an independent radiology review. Clinical information (palliative radiotherapy on-study, surgical excision of any lesion, details of paracentesis and thoracocentesis) must be provided to the BICR team.

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

If a patient has an unconfirmed PR or CR, an early scan is recommended 4 weeks later (e.g., if the initial observation of PR was seen at Week 9, a Week 13 scan should occur); subsequent tumor assessments must remain on the original assessment schedule (i.e., at Week 18, Week 27, Week 36, Week 45, etc.). For patients with unconfirmed progressive disease, subsequent tumor assessments must remain on the original assessment schedule (i.e., at Week 18, Week 27, Week 36, etc.), unless an early scan is clinically indicated.

ORR and PFS will be evaluated by a BICR as part of this clinical study. Images must be submitted to the BICR on the schedule outlined in the Study 17-214-09/CA045002 Imaging Manual. Patients who discontinue study treatment should continue to have tumor assessments until both BICR and Investigator's assessments of tumor images have determined progression or a subsequent anticancer therapy is started (Section 5.6). Patients who continue treatment beyond BICR-confirmed progression (Section 5.4.4) will continue to have tumor assessments until documentation of PD by the Investigator.

5.9 Pharmacokinetic, Biomarker, [redacted]

For Arm A, blood samples for PK analyses of NKTR-214, its metabolites, and nivolumab will be collected as described in Table 6.

Table 6: Pharmacokinetic, Biomarker, [redacted]

Study Day of Sample Collection (1 Cycle = 6 weeks)	Event	Time (Relative to Start of NKTR-214 Infusion) Hour: Min	NKTR-214 PK Blood Sample[d]	[redacted]	Nivolumab PK Blood Sample	[redacted]	CVA Biomarkers
Cycle 1 Day 1	Pre-dose	00:00	X	[redacted]	X	[redacted]	X[e]
	EOI[a]	00:30	X				
		4:00[b]	X				
Cycle 1 Day 3[c]		48:00	X				
Cycle 1 Day 5[c]		96:00	X				
Cycle 1 Day 8[c]		168:00	X				
Cycle 1 Day 22	Pre-dose	00:00	X	[redacted]	X	[redacted]	X[e]
Cycle 3 Day 1	Pre-dose	00:00	X	[redacted]	X	[redacted]	X[e]
	EOI[a]	00:30	X				
Cycle 4 Day 1	Pre-dose	00:00					X[e]
Cycle 6 Day 1	Pre-dose	00:00	X	[redacted]	X	[redacted]	X[e]
Cycle 9 Day 1	Pre-dose	00:00	X	[redacted]	X	[redacted]	X[e]
Cycle 12 Day 1	Pre-dose	00:00	X	[redacted]	X	[redacted]	X[e]
Cycle 15 Day 1	Pre-dose	00:00	X	[redacted]	X	[redacted]	X[e]
Safety Follow Up 1				[redacted]	X	[redacted]	
Safety Follow Up 2				[redacted]	X	[redacted]	
Time of CVA event							X[e]

CVA = cerebrovascular accident; EOI = end of infusion; [redacted]; TIA = transient ischemic attack

a. This sample should be taken immediately prior to the stopping NKTR-214 infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

b. Time window is ±1 hour for this sample (i.e., range 03:00 to 05:00 hours). Sample is preferred as close to 04:00 hours as is clinically feasible.

c. Time windows: -1 day for C1D3 (24-48 hours relative to start of NKTR-214 infusion), ± 1 day for C1D5 and -1 day for C1D8

d. [redacted]

e. [redacted] CVA and TIA biomarker samples will be obtained from patients from whom a Cycle 1 Day 1 biomarker sample has been collected (see Section 5.10.3).

Sites may only opt out of PK [redacted] sampling if they meet one of the following criteria: inability to process these samples, insufficient storage facilities, or unavailable courier pickup / dry ice.

5.9.1 Pharmacokinetics

For patients randomized to Arm A, blood samples for PK analysis will be collected and processed as outlined in a Laboratory Manual that will be provided to the site. All on-treatment time points are intended to align with days on which study drug is administered; if dosing occurs on a different day, the PK sampling should be adjusted accordingly. If it is known that a dose is going to be delayed, then the pre-dose sample should be collected just prior to the delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, an additional pre-dose sample should not be collected. All pre-dose samples should be collected within 24 hours before the start of any dose infusion.

For all PK blood samples, the date and actual time collected must be recorded. For patients whose only peripheral access is via a venous access device or peripherally inserted central catheter, refer to the Laboratory Manual for the proper technique to ensure undiluted whole blood for PK assessments.

Serum PK samples will be analyzed for nivolumab by a validated ligand binding assay. Plasma PK samples will be analyzed for NKTR-214-RC (related cytokines; mixture of compounds containing IL-2 independent of PEG conjugation status) and total PEG (mixture of compounds containing PEG independent of conjugation status to IL-2) by validated ligand binding assays as well as NKTR-214-AC (active cytokines; mixture of 2-PEG-IL-2, 1-PEG-IL-2, and free IL-2) by a qualified ligand binding assay.

[redacted]

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

5.10 Biomarkers

A variety of factors that could potentially predict clinical responses to NKTR-214 combined with nivolumab or to TKIs will be investigated in peripheral blood and in tumor specimens taken from all patients prior to, and on treatment and as outlined in Table 6 and the Schedule of Events (Table 1 through Table 4), respectively. Data from these investigations will be evaluated for associations with response, survival (OS, PFS), and/or safety (AE) if data allows. [redacted]
Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in the Laboratory Manual.

Sites may only opt out of biomarker sampling if they meet one of the following criteria: inability to process these samples, insufficient storage facilities, or unavailable courier pickup / dry ice.

5.10.1 Tumor Tissue Biopsy Collection

All patients must have tumor tissue identified and available to be sent during the Screening period:

- Most recent archival sample prior to randomization, from a site not previously irradiated and with no intervening treatment between time of acquisition and randomization

  OR

- A fresh pre-treatment biopsy obtained during the Screening Period.

Archival tissue should be provided in a formalin-fixed paraffin-embedded (FFPE) block or as unstained slides (minimum of 8 slides, preferably 20 slides) that have been sectioned within the 3 months prior to randomization. If 8 unstained slides are not available, fewer slides may be submitted; please contact the Medical Monitor for written approval. Leftover tissue blocks, but not slides, will be returned upon request.

Tumor samples must be a core biopsy, punch biopsy, excisional biopsy, or surgical specimen. Biopsy in bone lesion cannot be accepted. Fine needle aspirates/biopsy or other cytology specimens are insufficient for randomization. Biopsies of bone lesions that do not have a soft tissue component are also unacceptable for submission. Target lesions should not be biopsied unless there are no other lesions suitable for biopsy.

Collection of tissue samples in Cycle 1 between Days 14 and 21 and at the time of PD is optional but highly encouraged as they may help inform on the underlying biology of early

response/progression, and the biological mechanisms underlying acquired and/or de novo resistance to the drug(s) administered.

Pre-treatment tumor samples will be submitted for central PD-L1 IHC assessment. PD-L1 expression is defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 PharmDx 28-8 IHC assay. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 expression ≥ 1% or PD-L1 expression < 1% based on the frequency of tumor cell surface PD-L1 staining. Samples that have < 100 evaluable cells are considered not evaluable. Where membrane staining is obscured by high cytoplasmic staining, but the tumor tissue sample contains the minimum number of evaluable tumor cells, samples will be deemed PD-L1 indeterminate.

[redacted]

5.11 Medical Resource Utilization and Health Economics

Health care resource utilization data will be collected for all randomized patients using an internal case report form (CRF) developed for use in previous trials. The form, which is completed by study staff, records information about hospital admissions, including number of

days spent in various wards and discharge diagnosis, as well as non-protocol specified visits related to study therapy, including date of visit, reason for visit, and type of visit. The health care resource utilization data will be used to support subsequent economic evaluations.

5.12 Health-Related Quality of Life (HRQoL)

Patients will be asked to complete the NCCN/FACT Symptom Index for Kidney Cancer (FKSI-19), EQ-5D-3L, and selected items from the PRO-CTCAE. Refer to Section 7.6 for additional information.

5.13 Dosage Modification

Every effort should be made to follow planned dosing schedules for all study drugs in both treatment arms. Study drug administration may be delayed or modified for toxicity as described below and must be discontinued as required by criteria described in Section 5.14.

Dose modification for NKTR-214 and nivolumab in Arm A may be considered independently based on Investigator assessment of relationship of a toxicity to each of the study drugs. If only one of the study drugs meets the criteria for dose delay, then administration of the other study drug may be continued or delayed at the discretion of the Investigator. Likewise, in the event that one of the study drugs in Arm A is permanently discontinued due to toxicities, the other can continue to be administered.

Patients who require delay of nivolumab or NKTR-214 should be re-evaluated weekly or more frequently if clinically indicated and should resume treatment with combination of NKTR-214 and nivolumab when retreatment criteria are met (Section 5.13.7). Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. NKTR-214 and nivolumab are considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

For patients randomized to Arm A: NKTR-214 or nivolumab administration defines a scheduled nominal dosing visit (i.e., Cycle X Day 1, Cycle X Day 22). If a patient is assessed for an intended nominal dosing visit but study drug is not administered (e.g., due to an AE requiring dose delay, drug unavailable), any assessments performed during that visit should be recorded as "unscheduled." When study drug administration resumes, all assessments should be performed as scheduled for the next nominal dosing visit (i.e., Cycle X Day 1 or Cycle X Day 22 Visit).

For patients randomized to Arm B: Cycle 1 Day 1 is defined by the date that the first dose of sunitinib or cabozantinib is administered. Within a cycle, missed doses of sunitinib should be skipped and not replaced. Scheduled Cycle X Day 1 and Cycle X Day 22 visits are fixed relative to Cycle 1 Day 1, regardless of dose delays. If drug dosing is delayed at the time of these scheduled visits (e.g., due to an AE requiring dose delay, drug unavailable), the cycle visit is not shifted and all assessments should be performed as scheduled.

Tumor assessments for all patients should continue as per protocol even if dosing is delayed.

5.13.1 NKTR-214 Dose-Delay and Reduction Criteria

Dose delays and reductions are permitted for NKTR-214. NKTR-214 may be delayed or reduced to 0.003 mg/kg based on observed drug-related toxicities. If the NKTR-214 dose is reduced to 0.003 mg/kg, the dose level should remain at this level throughout the remainder of the study.

NKTR-214 should be delayed for the following reasons:

- For persistent Grade 2 related toxicity, a dose delay or dose reduction may be implemented at the discretion of the Investigator.
  - Grade ≥ 2 creatinine increase
    - For patients who must delay study treatment due to Grade ≥ 2 creatinine increase due to a non-inflammatory cause, delay retreatment with study drug for approximately 3 to 5 days. After the dosing delay, the patient may resume study drug when serum creatinine has returned to Grade ≤ 1, as assessed within 24 hours prior to redosing. For further guidance, refer to renal adverse event management algorithm in current Nivolumab Investigator's Brochure.
- Grade ≥ 3 toxicity at least possibly related to NKTR-214: NKTR-214 must be delayed until resolution to Grade 1 or baseline (unless otherwise requiring permanent discontinuation, per Section 5.14.1.1) with the following exceptions:
  - Grade ≥ 3 lymphopenia
  - Grade ≥ 3 asymptomatic amylase or lipase elevation
- Patient has acute infection (e.g., fever, upper or lower respiratory tract infection) requiring systemic antibiotic therapy. Patient may resume study treatment once free of signs or symptoms for 72 hours after completion of antibiotic therapy (See Section 5.13.7).
- 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 dose or at a lower dose level when toxicity resolves to Grade 1 or returns to baseline, except for instances where the potential recurrence of the event poses an undue risk for the patient. Medical Monitor consultation is required for dose reduction.

5.13.2 Nivolumab Dose-Delay and Reduction Criteria

Dose reductions for nivolumab are not permitted in this study.

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or total bilirubin abnormalities

- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, and/or total bilirubin will require dose discontinuation (unless satisfying the Cycle 1 ALT/AST elevation criteria outlined in Section 5.13.3)
- Patient has acute infection (e.g., fever, upper or lower respiratory tract infection) requiring systemic antibiotic therapy. Patient may resume study treatment once free of signs or symptoms for 72 hours after completion of antibiotic therapy (See Section 5.13.7).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

Patients who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when retreatment criteria are met.

5.13.3 Dose-Modification Criteria for NKTR-214 and Nivolumab 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 judgment. Subsequent cycles should follow standard Hepatic Adverse Event Management Algorithm (see the nivolumab Investigator's Brochure).

Rule out non-inflammatory etiologies. If non-inflammatory cause, treat accordingly and continue NKTR-214 and nivolumab. 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 + nivolumab)

Increase frequency of liver function test (LFT) monitoring to approximately every 3 days and delay treatment until lab abnormalities resolve to Grade 1 or baseline.

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 + nivolumab)

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

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

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

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

Please refer to Section 5.14 for discontinuation criteria.

5.13.4 Monitoring and Management of Elevated Hepatic Transaminases

Elevated hepatic transaminases are an overlapping toxicity that can occur for both NKTR-214 and nivolumab. The elevations in hepatic transaminases associated with NKTR-214 typically occur at the time of peak active cytokine concentration in the blood (Days 4-8) and are often accompanied by other IL-2 mediated AEs such as flu-like symptoms, rash or pruritus. The transient elevations in hepatic transaminases are usually asymptomatic, mild or moderate in severity, not associated with increased total bilirubin and alkaline phosphatase, resolve spontaneously without treatment, and predominantly occur in Cycle 1 and Cycle 2; the transaminase elevations are considered to occur in the context of IL-2 mediated AEs. For transaminase elevations occurring in Cycle 1 consistent with a cytokine-related effect without alternative etiologies, follow the Cycle 1 hepatic adverse event management guideline (Section 5.13.3).

Hepatic events, including elevated LFTs, have also been observed for nivolumab. Most cases were of low or moderate severity. Higher grade abnormalities are concerning for immune-mediated hepatitis, and typically occur with a later onset (median time to onset of 3.3 months). Immune-mediated hepatitis generally results in a quick rise in LFTs 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 nivolumab Investigator's Brochure or product labeling for appropriate management.

5.13.5 Monitoring and Management of Adrenal Insufficiency and Hypophysitis

Adrenal insufficiency and hypophysitis have been observed in patients receiving NKTR-214 and nivolumab. Consider prompt evaluation when patients have signs or symptoms of hypophysitis or adrenal insufficiency which includes levels of early-morning adrenocorticotropic hormone, cortisol, thyroid stimulating hormone (TSH), and free thyroxine (T4). Co-management with an endocrinologist is recommended for patients with pre-existing adrenal insufficiency.

5.13.6 Monitoring and Management of Eosinophilia

5.13.6.1 NKTR-214-induced Eosinophilia

Frequent and significant eosinophilia has been observed in patients receiving NKTR-214, primarily starting at Cycle 2 with levels plateauing after Cycle 3, consistent with the known pharmacodynamic effect of IL-2 therapy. The eosinophilia pattern demonstrates a cyclic waxing and waning pattern whereby eosinophil levels peak approximately 7 days after each infusion and wane before the patient's next infusion. Isolated cases of hypereosinophilic syndrome and other eosinophilic disorders have been reported.

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

5.13.6.2 Eosinophilic Disorders

Isolated cases of hypereosinophilic syndrome and drug reaction with eosinophilia and systemic symptoms have been reported. If there is clinical concern for an eosinophilic disorder, the Investigator is encouraged to contact the Medical Monitor.

Additional details regarding eosinophilia and eosinophilic disorders are provided in the NKTR-214 Investigator's Brochure.

5.13.7 Criteria to Resume NKTR-214 and/or Nivolumab

Patients will be permitted to resume study drug(s) at the same dose level(s) following resolution of an AE to Grade ≤ 1 or to baseline within 8 weeks after the last dose unless the Medical Monitor is consulted and agrees with the rationale for resuming therapy after 8 weeks, and with the exception of patients who meet criteria for permanent discontinuation as specified in Section 5.14.1.1. If patients required steroids to treat an AE, the taper must be completed and dose should be < 10 mg prednisone per day. Patients who meet criteria for permanent discontinuation must not receive further study therapy.

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

- Patients who delayed dosing for acute infection requiring systemic antibiotic therapy must be free of signs or symptoms of infection for 72 hours after completion of antibiotic therapy prior to resuming study treatment.
- Patients may resume study treatment in the presence of Grade 2 fatigue
- Patients who have not experienced a Grade 3 drug-related skin AE may resume study treatment in the presence of Grade 2 skin toxicity
- For patients with Grade 2 AST, ALT, 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. Patients 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 the Medical Monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor. Grade ≥ 3 adrenal insufficiency or Grade ≥ 4 hypophysitis require discontinuation regardless of control with hormone replacement (see Section 5.14.1 for permanent treatment discontinuation criteria). Hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should not require discontinuation.
- For patients who must delay study treatment due to Grade ≥ 2 creatinine increase due to a non-inflammatory cause (see Sections 5.13.1 and 5.13.2) delay retreatment with study drug for approximately 3 to 5 days. After the dosing delay, the patient may resume study drug treatment when serum creatinine has returned to Grade ≤ 1, as assessed within 24 hours, or as soon as locally feasible, except where permanent discontinuation of study drug is required (see Section 5.14.1.1).

Dose delay of NKTR-214 combined with nivolumab that results in treatment delay of > 8 weeks requires treatment discontinuation, with exceptions as noted in Section 5.14.1.1. However, if the toxicity resolves to Grade ≤ 1 or baseline > 8 weeks after the last dose, but the patient does not otherwise meet the criteria for permanent discontinuation (see Section 5.14.1.1), and the Investigator believes that the patient is deriving clinical benefit, then the patient may be eligible to resume the study drug(s) following the approval of the Medical Monitor.

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

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

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and NKTR-214 are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated

with immuno-oncology agents may mitigate severe toxicity. Management Algorithms including the use of systemic corticosteroids (see the nivolumab Investigator's Brochure) have been developed to assist Investigators in assessing and managing the following groups of AEs (including, but may not be limited to):

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological (see Appendix 6)
- Myocarditis

5.13.8.2 Cytokine Release Syndrome

Events of CRS have been reported after NKTR-214 exposure (5 patients). The majority of CRS events reported in these trials were Grade 1 or Grade 2 and resolved. Two Grade 3 events of CRS were reported and resolved. These cases either co-reported IL-2 mediated symptoms or were confounded (i.e., infectious etiology).

CRS is a clinical diagnosis with a constellation of symptoms often characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. In addition, diarrhea and end organ dysfunction can be seen in CRS. Many of these symptoms overlap with known AEs seen in NKTR-214 and nivolumab combination therapy (i.e., pyrexia and hypotension). These symptoms may be seen in infusion reactions as well as other known syndromes, such as tumor lysis syndrome and macrophage activation syndrome.

Manifestations of infusion reactions are provided in Section 5.13.9.

For suspected cases of CRS Grade 3 or higher, the Investigator is encouraged to contact the Medical Monitor. An algorithm for CRS management is provided in Appendix 7.

5.13.9 Treatment of NKTR-214 or Nivolumab-Related Infusion Reactions

Infusion reactions have been reported during infusions with NKTR-214 and nivolumab. If such a reaction were to occur with either the NKTR-214 or nivolumab infusion, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Infusion reactions should be graded as outlined below (consistent with Common Terminology Criteria for Adverse Events [CTCAE] v5.0 grading of infusion-related reaction; please also refer to Section 8.3).

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. Subsequent infusions may be administered at a reduced rate (e.g., 50% of the original infusion rate).

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

- Stop the NKTR-214 or nivolumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at the bedside and monitor the patient until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. If symptoms recur after restarting the NKTR-214 or nivolumab infusion, then no further drug will be administered at that visit. Administer diphenhydramine 50 mg IV, remain at the bedside, and monitor the patient until resolution of symptoms.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg administered at least 30 minutes before the infusion. If necessary, corticosteroids (up to 25 mg of methylprednisolone or equivalent) may be used (see Appendix 5 for corticosteroid dose equivalents). Subsequent infusions may be administered at a reduced rate (e.g., 50% of the original infusion rate).

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

- Immediately discontinue infusion of NKTR-214 or nivolumab. 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. NKTR-214 or nivolumab will be permanently discontinued. The patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at the bedside and monitor the patient until recovery of the symptoms.

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

5.13.10 Sunitinib or Cabozantinib Dosing-Delay Criteria

Sunitinib or cabozantinib dosing should be delayed for the following:

- If UPCR ≥ 2.0 [≥ 227 mg/mmol] urine dipstick protein ≥ 3+, obtain 24-hour urine protein to determine if dosing should be delayed.
  - Dosing may proceed if 24-hour urine protein < 3 g.
  - Delay dosing if 24-hour urine protein ≥ 3 g (see Section 5.13.11 for criteria to resume).
  - Recurrent 24-hour urine protein ≥ 3 g after dose reduction requires study drug discontinuation (refer to Sections 5.14.1.2 and 5.14.1.3).
- Clinical manifestations of CHF
- LVEF > 20% but < 50% below baseline
- Any Grade 2 drug-related hemorrhage
- Any Grade 2 or 3 drug-related venous thrombosis requiring anticoagulation, with the following exception:
  - Any recurrent or worsening venous thromboembolic event after restarting sunitinib or cabozantinib will require discontinuation
- Any Grade 3 drug-related adverse event or Grade 3 drug-related laboratory abnormality (e.g., AST, ALT, total bilirubin) that persists for more than 1 week or worsens despite supportive care management, with the following exceptions:
  - Grade ≥ 2 drug-related arterial thromboembolic events, including cerebrovascular ischemia, cardiac ischemia, or peripheral or visceral arterial ischemia, require discontinuation.
  - Grade ≥ 3 drug-related hemorrhage requires discontinuation (Section 5.14.1.2).
  - Drug-related AST or ALT > 8 × ULN requires discontinuation (Section 5.14.1.2).

  - Concurrent AST or ALT > 3 × ULN (> 2 × baseline AND > 3 × ULN for patients with baseline elevation) and total bilirubin > 2 × ULN (> 2 × baseline AND > 2 × ULN for patients with baseline elevation), consistent with potential drug-induced liver injury (see Section 8.10), requires discontinuation.
  - Grade 3 drug-related amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require dose delay. In such cases, more frequent monitoring (e.g., weekly) of amylase and lipase is recommended. If amylase or lipase worsens to Grade 4 severity or the patient develops symptoms or clinical manifestations of pancreatitis, dosing should be delayed.

- Sustained Grade 3 drug-related hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Note: Stopping or reducing the dose of sunitinib or cabozantinib is expected to cause a decrease in blood pressure. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly.
- Grade 4 drug-related amylase or lipase abnormalities require dose delay. Patients should be monitored for development of symptoms or clinical manifestations of pancreatitis.
- Grade 4 drug-related electrolyte abnormalities require dose delay. Electrolyte correction with supplementation/appropriate management should be promptly initiated.
- Grade 4 drug-related neutropenia, lymphopenia, leukopenia, anemia, or thrombocytopenia
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying sunitinib or cabozantinib dosing
- For patients scheduled for major surgery, including dental surgery which may impact bone healing, sunitinib or cabozantinib dosing should be delayed at least 28 days prior to scheduled surgery. The treating physician should use clinical judgment with regard to the risks and benefits of the planned surgical procedure if it is not possible to delay cabozantinib or sunitinib dosing for 28 days prior to the procedure. A delay of cabozantinib and sunitinib dosing of 5 to 7 days is recommended for healing for minor surgery.

As a general approach, all AEs related to sunitinib or cabozantinib should be managed with supportive care, when possible, at the earliest signs of toxicity. Calcium, magnesium, potassium, and phosphorus should be kept above the lower limits of the laboratory normal values. Please refer to the sunitinib or cabozantinib prescribing information for additional information regarding dose modifications and AE management.

5.13.11 Criteria to Resume Sunitinib or Cabozantinib

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

- Patients may resume dosing in the presence of Grade 2 fatigue.

- Patients who delayed dosing due to 24-hour urine protein ≥ 3.0 g may resume dosing at one dose level reduction when UPCR < 2.0 [< 227 mg/mmol]. Repeat episodes of urine protein ≥ 3 g despite dose reductions require study drug discontinuation (refer to Section 5.14.1.2).
- Patients who delayed dosing due to Grade 3 hypertension may resume dosing at the same dose or at one dose level reduction, at the discretion of the Investigator, when hypertension has improved to Grade ≤ 2.
- Patients who delayed dosing due to Grade 4 lipase or amylase abnormalities may resume dosing upon resolution to Grade ≤ 2.
- Patients who develop a pulmonary embolism and/or DVT should have study treatment delayed until therapeutic anticoagulation is established. Treatment with sunitinib may be resumed in patients with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the patient is deriving clinical benefit from sunitinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the Investigator.
- Patients who delayed dosing due to ≤ Grade 2 hemorrhage may resume dosing if bleeding is under control (recovered to at least Grade 1 level) and has a low risk of recurrence.
- Patients who delayed dosing due to major surgery should not resume sunitinib until complete wound healing has taken place. Following sunitinib resumption, patients should be monitored for wound dehiscence, wound infections, and other signs of impaired wound healing.

5.13.12 Sunitinib or Cabozantinib Dose Reduction and Escalation

Table 7 outlines the permitted doses for sunitinib and cabozantinib.

Table 7: Sunitinib and Cabozantinib—Permitted Doses

	Sunitinib	Cabozantinib
0 (starting dose)	50 mg daily	60 mg daily
-1	37.5 mg daily	40 mg daily
-2	25 mg daily	20 mg daily

5.13.12.1 Sunitinib

Sunitinib dose reductions are permitted as per the approved product label for safety reasons or when a concomitant strong cytochrome P450 3A4 (CYP3A4) inhibitor is needed (Appendix 8). Selection of an alternative concomitant medication with minimal or no enzyme inhibition potential is recommended whenever possible.

After toxicity requiring a dose delay has improved and meets the criteria to resume dosing (Section 5.13.11), patients should resume sunitinib at one dose level reduction. Dose reductions

should occur in 12.5 mg decrements. No more than 2 dose reductions are allowed. If more than two dose reductions are necessary (i.e., reduction to less than 25 mg daily), the patient must be permanently discontinued (Section 5.14.1.2).

Patients who required a dose delay due to Grade 3 hypertension, which improved with antihypertensive medications, or any Grade 2 or 3 drug-related adverse event or asymptomatic laboratory abnormality that improved to Grade ≤ 1 within 7 days with supportive medical care may resume sunitinib at the same dose or a reduced dose, at the discretion of the Investigator.

Patients who required a dose delay due to 24-hour urine protein ≥ 3 g, may resume study treatment at a reduced dose once UPCR is < 2 (< 227 mg/mmol). Repeat episodes of urine protein ≥ 3 g despite dose reductions require study drug discontinuation (refer to Section 5.14.1.2).

At the time a dose reduction is considered, also refer to Section 5.13.10 for dose delay recommendations and Section 5.14 for discontinuation criteria.

Sunitinib dose re-escalations are permitted as per the approved product label when a concomitant CYP3A4 inducer is needed (Appendix 8); however, escalation above the starting dose is not allowed. Selection of an alternative concomitant medication with minimal or no enzyme induction potential is recommended whenever possible.

5.13.12.2 Cabozantinib

Reduce the starting dose of cabozantinib to 40 mg once daily in patients with moderate hepatic impairment (i.e., Child-Pugh Class B); refer to the cabozantinib (Cabometyx®) US Prescribing Information and/or the corresponding SmPC for updated dosing guidance or further information. For patients receiving a concomitant strong CYP3A4 inducer or inhibitor, follow the dosing guidelines in the Package Insert, SmPC, or local health authority guidelines applicable to your country.

Dose reductions for adverse event management are allowed for cabozantinib (Table 7). Cabozantinib doses will not be re-escalated once reduced, unless a concomitant strong CYP3A4 inducer is started (see Section 5.13.12.3); however, escalation above the starting dose is not allowed.

After toxicity requiring a dose delay has improved and meets the criteria to resume dosing (Section 5.13.11), patients who were receiving cabozantinib 40 mg daily prior to the delay will resume cabozantinib at 20 mg daily. If more than 2 dose reductions are necessary (i.e., reduction to less than 20 mg daily) or more than 1 dose reduction in patients with Child-Pugh Class B (i.e., starting dose 40 mg daily), cabozantinib must be permanently discontinued (Section 5.14.1.3).

Patients who required a dose delay due to 24-hour urine protein ≥ 3 g, may resume study treatment at a reduced dose once UPCR is < 2 [< 227 mg/mmol]. Recurrent 24-hour urine protein ≥ 3 g after dose reduction requires study drug discontinuation (refer to Section 5.14.1.3).

Patients who required a dose delay due to Grade 3 hypertension, which improved with antihypertensive medications, or any Grade 2 or 3 drug-related adverse event or asymptomatic laboratory abnormality that improved to Grade ≤ 1 within 7 days with supportive medical care may resume cabozantinib at the same dose or a reduced dose, at the discretion of the Investigator.

Patients with asymptomatic Grade 2 drug-related AST, ALT or total bilirubin elevation, or Grade 3 drug-related lipase or amylase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis may reduce cabozantinib by 1 dose level, without delaying dosing, at the discretion of the Investigator.

5.13.12.3 For Patients Who Start Taking a Concomitant Strong CYP3A4 Inhibitor

Reduce the daily dose of cabozantinib or sunitinib by one dose level. Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor (see Prescribing Information for cabozantinib and sunitinib).

5.14 Discontinuation Criteria

5.14.1 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.
- 2 years since Cycle 1 Day 1 (Arm A only)
- Any clinical 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
- See additional study treatment discontinuation criteria specific to NKTR-214 and nivolumab (Section 5.14.1.1), sunitinib (Section 5.14.1.2), and cabozantinib (Section 5.14.1.3) due to AEs.
- 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 (e.g., 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
- 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 mRECIST 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 by both the BICR and Investigator's assessment or begins a subsequent anticancer therapy).

A patient may also be withdrawn from investigational product/study by the Sponsor, Regulatory Authorities, or IRBs/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 (Table 4) 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 8.12.2 (Pregnancy).

All patients who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Table 4. 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 (i.e., 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 CRF page.

5.14.1.1 NKTR-214 Combined with Nivolumab Discontinuation Criteria

Patients meeting any of the following criteria will be required to permanently discontinue all assigned study drug(s). However, per Investigator assessment, NKTR-214 or nivolumab may be

continued as a monotherapy if the toxicities listed below are considered related to only one of the study drugs, once the criteria to resume are met (Section 5.13.7). For CVA events and suspected TIA events, follow the criteria described below (additional details are provided in the CVA management algorithm in Appendix 6).

NKTR-214 combined with nivolumab treatment should be permanently discontinued for the following:

- Any ≥ Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the retreatment period OR requires systemic treatment
- Grade 3 or 4 infusion reaction of any duration that occurs during the:
  - NKTR-214 infusion or prior to the nivolumab infusion requires discontinuation of NKTR-214.
  - Nivolumab infusion or later requires discontinuation of both NKTR-214 and nivolumab.
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, and endocrinopathies
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, or hypersensitivity reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies (excluding adrenal insufficiency) adequately controlled with only physiologic hormone replacement do not require discontinuation.
    - Note: For adrenal insufficiency of Grade ≥ 3, treatment needs to be discontinued regardless of control with hormone replacement (hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should not require discontinuation).
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related LFT abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm, in nivolumab Investigator's Brochure):
      - ♦ Treatment-emergent ALT or AST > 3 times ULN (> 2 × baseline AND > 3 × ULN for patients with baseline elevation) AND
      - ♦ Total bilirubin > 2 times ULN (> 2 × baseline AND > 2 × ULN for patients with baseline elevation) or clinical jaundice, without initial findings of cholestasis (e.g., elevated serum alkaline phosphatase) (see Section 8.10)

In most cases of Grade 3 AST or ALT elevation that do not improve with hepatic AE management, study treatment will be permanently discontinued (see Section 5.13 for more details). If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the Investigator and the Medical Monitor must occur. For IL-2 mediated ALT/AST elevations < 8.0 × ULN in Cycle 1 only, study treatment does not need to be discontinued.

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - 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 adverse events (except adrenal insufficiency or hypophysitis), such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor.
  - Note: For Grade ≥ 3 adrenal insufficiency and/or Grade ≥ 4 hypophysitis, treatment needs to be discontinued regardless of control with hormone replacement (hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should not require discontinuation).
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a patient with a dosing delay lasting > 8 weeks, the Medical Monitor must be consulted and agree with the rationale for resuming therapy. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 3 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing.
- Any new CVA event confirmed by imaging (diffusion-weighted imaging [DWI] MRI preferred unless contraindicated), regardless of neurological symptoms, and for suspected TIA without clear alternative etiology (see Appendix 6).

5.14.1.2 Sunitinib Discontinuation Criteria

Treatment with sunitinib should be permanently discontinued for any of the following:

- Any requirement for more than 2 sunitinib dose reductions
- Any Grade drug-related arterial thrombosis
- Grade ≥ 3 drug-related hemorrhage or recurrent Grade 3 drug-related hemorrhage after dose reduction
- Grade 4 drug-related symptomatic venous thrombosis
- LVEF reduction ≥ 50% from baseline
- Grade 4 drug-related cardiac toxicity
- Any other Grade ≥ 2 drug-related arterial or venous thromboembolic events including cerebrovascular ischemia, cardiac ischemia, or peripheral or visceral arterial ischemia
- Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis or necrotizing fasciitis
- Thrombotic microangiopathy
- Nephrotic syndrome or repeat episodes of urine protein ≥ 3 g despite dose reductions
- Angioedema due to hypersensitivity
- Two or more symptomatic episodes of hypertension despite modification of antihypertensive medication(s) and reduction of sunitinib dose
- Any drug-related LFT abnormality that meets the following criteria require discontinuation:
    - Treatment-emergent ALT or AST > 3 times ULN (> 2 × baseline AND > 3 × ULN for patients with baseline elevation)
    - Total bilirubin > 2 times ULN (> 2 × baseline AND > 2 × ULN for patients with baseline elevation) or clinical jaundice, without initial findings of cholestasis (e.g., elevated serum alkaline phosphatase) (see Section 8.10)
    - Sunitinib should be interrupted for Grade 3 or 4 drug-related hepatic adverse reactions and discontinued if there is no resolution within 7 days. Sunitinib should be permanently discontinued if a patient subsequently experiences Grade 3 or 4 changes in LFT or have other signs and symptoms of liver failure.
- Any dosing delay lasting > 8 weeks unless the Medical Monitor is consulted and agrees with the rationale for resuming therapy after a delay > 8 weeks. Note that tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued sunitinib dosing.

5.14.1.3 Cabozantinib Discontinuation Criteria

Permanently discontinue cabozantinib for patients with any of the following:

- Any requirement for more than 2 cabozantinib dose reductions (i.e., reduction to less than 20 mg)
- Acute myocardial infarction or new CVA event (including TIA) confirmed by imaging (DWI MRI preferred; refer to Appendix 6)
- Any other Grade ≥ 2 drug-related arterial or venous thromboembolic events including cerebrovascular ischemia, cardiac ischemia, or peripheral or visceral arterial ischemia
- LVEF reduction ≥ 50% from baseline
- Any Grade ≥ 3 hemorrhage
- Grade 4 hypertension or persistent Grade 3 hypertension despite optimal medical management and cabozantinib dose reduction
- Reversible posterior leukoencephalopathy syndrome
- Development of GI perforation or drug-related fistula
- Nephrotic syndrome or recurrent nephrotic range proteinuria (i.e., recurrent 24-hour urine protein ≥ 3 g after dose reduction)
- Any drug-related LFT abnormality that meets the following criteria requires discontinuation:
  - Treatment-emergent ALT or AST > 3 times ULN (> 2 × baseline AND > 3 × ULN for patients with baseline elevation)
  - Total bilirubin > 2 times ULN (> 2 × baseline AND > 2 × ULN for patients with baseline elevation) or clinical jaundice, without initial findings of cholestasis (e.g., elevated serum alkaline phosphatase) (see Section 8.10)
- Any Grade 4 drug-related adverse event or laboratory abnormality, with the following exceptions:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
  - Isolated Grade 4 electrolyte abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing delay lasting > 8 weeks unless the Medical Monitor is consulted and agrees with the rationale for resuming therapy after a delay > 8 weeks. Note that tumor assessments should continue as per protocol even if dosing is delayed.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued cabozantinib dosing.

5.15 Prior and Concomitant Medications

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

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 30 days prior to randomization through the last Safety Follow-Up Visit will be documented and recorded, including start and stop date, dose and route of administration, frequency, and indication. Medications taken for a procedure (e.g., biopsy) should also be included.

5.15.1 Premedication

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

If a patient experiences a Grade 1-2 infusion reaction during any infusions with NKTR-214 or nivolumab, prophylactic premedications may be administered for subsequent infusions (see Section 5.13.9 for further details on management and prevention of infusion reactions).

Please refer to Section 5.15.2 for additional recommendations on prophylaxis.

5.15.2 Permitted Concomitant Treatment

5.15.2.1 Steroids

Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Patients with pre-existing adrenal impairment requiring corticosteroid supplementation may be at increased risk for hypotensive episodes during treatment with NKTR-214 and may require co-management with an endocrinologist (see Section 5.13.5). A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., pneumonia, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Use of corticosteroids for the management of autoimmune conditions (as outlined in the Investigator's Brochure for nivolumab) is permitted.

5.15.2.2 Prophylaxis

Prophylaxis for flu-like symptoms with either acetaminophen (paracetamol) or ibuprofen is permitted on study per the Investigator's discretion. Prophylaxis for flu-like symptoms (acetaminophen or non-steroidal anti-inflammatory agents) can be initiated on either the day of NKTR-214 administration or the day after administration and may continue for 4 days after administration or longer as needed.

Prophylaxis for rash and/or pruritus with anti-histamines is permitted on study per the Investigator's discretion. Prophylaxis for rash and/or pruritus can be initiated on either the day of NKTR-214 administration or the day after administration and may continue for 4 days after administration or longer as needed.

Prophylactic use of antibiotics for signs of potential asymptomatic urinary tract infection is permitted.

5.15.2.3 Palliative and Supportive Care

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted if required but should be avoided unless the patient has a BICR-confirmed progression. Palliative therapy must be clearly documented as such in the study record and shared with the BICR vendor if performed prior to BICR-confirmed disease progression.

Concomitant palliative and supportive care for disease-related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed.

5.15.3 Prohibited and/or Restricted Concomitant Medications

5.15.3.1 Prohibited Medications

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.15.2) defined as a daily dose of greater than 10 mg prednisone equivalents
- Any antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or investigational agent) is prohibited during the study.
- Any botanical preparation (e.g., herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

- Any live / attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio, and measles-mumps-rubella, or Flumist® Quadrivalent) during treatment and until 100 days post last dose of nivolumab. Note: all vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19) are allowed on treatment. For any questions about the COVID vaccines, please contact the Medical Monitor.

5.15.3.2 Blood Pressure Medications

Consideration should be given to withholding antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (e.g., alpha blockers for benign prostatic hypertrophy) prior to each dose of NKTR-214, particularly when therapy involves multiple antihypertensive drugs and classes other than thiazide diuretics. If withholding antihypertensive medications, withhold no less than 12 hours and no more than 48 hours prior to each dose of NKTR-214.

Patients who are on medications with antihypertensive effects for the treatment of coronary artery disease (e.g., β-blockers, Ca channel blockers, nitrates, etc.) should be able to withhold these drugs prior to initiation of treatment (i.e., based on blood pressure monitoring results).

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

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

5.15.3.3 Anticoagulation

Patients with a history of a venous or arterial thromboembolic event must be receiving a stable regimen of therapeutic anticoagulation (preferably LMWH or DOAC). Unless there is a new medical contraindication observed after Cycle 1 Day 1, a patient with a history of venous or arterial thromboembolic event must be maintained on therapeutic anticoagulation throughout the patient's participation on study (i.e., through discontinuation of all study drugs).

Use of coumadin is permitted; however, therapeutic dosing should target a specific international normalized ratio (INR) stable for at least 4 weeks prior to randomization. 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.

Acetylsalicylic acid should not be combined with LMWH or DOAC due to increased risk of hemorrhage.

5.15.3.4 Cytochrome P450 Potential Drug Interactions

Sunitinib and cabozantinib are metabolized by CYP3A4. Co-administration of strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, dexamethasone, and St. John's Wort) may significantly decrease sunitinib or cabozantinib concentrations and chronic use of CYP3A4 inducers must be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a patient who has been concurrently receiving a stable dose of sunitinib or cabozantinib, as this could significantly increase the exposure to sunitinib or cabozantinib. Co-administration of strong inhibitors of the CYP3A4 family (Appendix 8) may significantly increase sunitinib or cabozantinib concentrations and may increase the risk of toxicities related to these study drugs. If alternative concomitant therapies are not available, doses or sunitinib or cabozantinib may be interrupted or reduced to mitigate the risk of increased toxicities (see Sections 5.13.12.1 and 5.13.12.2). Grapefruit, grapefruit juice, and other foods that are known to inhibit CYP3A4 should be avoided during treatment with sunitinib or cabozantinib.

5.15.3.5 Effect of NKTR-214 on PK of Concomitant Medications

NKTR-214 causes transient increases in circulating cytokines lasting for about one week after NKTR-214 dosing in the q3w dosing schedule. Several of these cytokines (IFN-γ, IL-6, IL-10) have the potential to decrease the activity of multiple drug metabolizing enzymes and drug transporters. Consequently, treatment with NKTR-214 may lead to a temporary decrease in clearance of drugs that are substrates of metabolizing enzymes or drug transporters. Where indicated based on decreased tolerability or the occurrence of adverse effects related to a concomitant drug, reduce the dosage of the concomitant drug per the product label during Days 3 to 8 of each cycle of NKTR-214.

5.15.3.5.1 Potential 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.

5.16 Adverse Events

All AEs, either reported by the patient or observed by study staff, will be recorded until the last Safety Follow-up Visit (see Section 5.6). This study will use the Medical Dictionary for Regulatory Activities (MedDRA) for coding all AEs. AEs will be summarized by preferred term, system organ class, grade of severity, and relationship to each study drug (NKTR-214 and/or nivolumab and/or sunitinib and/or cabozantinib).

5.17 Treatment Assignment and Patient Number Assignment

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.

An Interactive Response Technology (IRT) will be employed to manage patient randomization. Randomization stratification factors are described in Section 5.1.

For all countries, Nektar will supply NKTR-214 and nivolumab from a central source. With Sponsor approval, and depending on local health authority guidelines and drug availability, nivolumab, sunitinib, and cabozantinib may be obtained through commercial supply, the site pharmacy, or through a central source. Sunitinib and cabozantinib must both be approved by the local Competent Authority and commercially available (local sourcing of these agents may be permitted on an ad hoc basis). Choice of TKI for an individual patient randomized to Arm B will depend on what drug products are available at each medical center and the Investigator's choice. Selection of a drug product should be based on what would have been offered to that patient, should the patient not be participating in this trial. Agents that are not routinely available in the pharmacy at each medical center will not be considered "available therapy." The Investigator must have prior clinical experience with the control arm for the treatment of a patient with renal cell carcinoma.

6.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

Table 8 provides the study treatments that will be administered in the study. Not all of the capsule/tablet strengths for sunitinib and cabozantinib may be available. Final available capsule/tablet strengths will be listed in the Pharmacy Manual.

Table 8: Investigational Products

Product Description	Strength	Packaging / Appearance	Storage Conditions
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

6.1 NKTR-214

6.1.1 Drug Description and Formulation

[redacted]

6.1.2 Drug Packaging and Labeling

[redacted] Each

vial will be labeled with the study drug number/name, strength, name of the Sponsor, storage condition, lot number, and the required cautionary statement.

6.1.3 Drug Reconstitution and Handling

[redacted]

Refer to the Pharmacy Manual for detailed handling and administration information.

6.1.4 Drug Storage

[redacted]

6.1.5 Drug Shipment

[redacted]. Refer to the Pharmacy Manual for additional details for ordering drug supply.

6.2 Nivolumab, Sunitinib, and Cabozantinib Formulation, Preparation, Storage, and Packaging

Refer to the Pharmacy Manual for details.

6.3 Study Drug Accountability and Reconciliation

NKTR-214 and nivolumab will be supplied to the Investigator by Nektar Therapeutics or its designee. With Sponsor approval, and depending on local health authority guidelines and drug availability, nivolumab, sunitinib, and cabozantinib may be obtained through commercial supply, the site pharmacy, or through a central depository. Depending on source of supply per specific country requirements, the packaging and labeling may vary. Products will be labeled to meet local country requirements. Please refer to the Pharmacy Manual for detailed information.

Study drug supplies must be kept in an appropriate, secure, locked area and stored in accordance with the conditions specified on the labels. Depending on local health authority guidelines, intravenous fluids and associated supplies (IV administration sets, in-line filters, calibrated pumps) may be obtained through commercial supply, the site pharmacy, or through a central depository.

The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to Nektar Therapeutics. In addition, (for those patients randomized to Arm B), the patient must agree to complete a pill

diary to record oral dosing, which will be reviewed by the Investigator or designee at the beginning of each cycle, starting with Cycle 2.

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

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

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

7.0 ASSESSMENT OF EFFICACY

Response and progression will be determined by BICR using mRECIST 1.1.

7.1 Imaging Assessments for the Study

Images will be submitted to an imaging core lab and will be reviewed by the BICR on an ongoing basis. Sites should be qualified prior to scanning the first patient and understand the image acquisition guidelines and submission process as outlined in the Study 17-214-09/ CA045002 Imaging Manual provided by the imaging core lab.

Tumor assessments should be acquired as outlined in Section 1.2 (Schedule of Events) and as described below.

- For patients who are on treatment, contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis, and all other known and suspected sites of disease should be performed every 9 weeks (± 7 days) from randomization through (and inclusive of) Week 54 and then every 12 weeks (± 7 days).
    - Tumor assessment schedule is relative to the date of randomization and will be maintained regardless of dose delays.
- Patients who have not progressed, as determined by both BICR and Investigator assessment, should continue tumor assessments according to the protocol-specified schedule, or sooner if clinically indicated.
- If patients discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol-specified schedule, as noted in Section 1.2, until progression has been confirmed by both BICR and Investigator assessment.
- Patients who are treated beyond Investigator-assessed disease progression should continue tumor assessments until the criteria for treatment discontinuation are met and BICR-assessed progression has occurred.
- Tumor assessments are no longer required if subsequent anticancer therapy is started, even if the patient has not yet progressed.

Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI and bone scan should be submitted to central imaging vendor. X-Ray scans that clearly demonstrate interval progression of disease, most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, radiographs do not need to be submitted centrally.

7.2 Methods of Measurement

Contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis, and all other known and suspected sites of disease should be performed for tumor assessments.

Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each patient using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same Investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the mRECIST 1.1 criteria.

Should a patient have contraindication for CT intravenous contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a patient have contraindication for both MRI and CT intravenous contrasts, a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a patient have contraindication for MRI (e.g., incompatible pacemaker) in addition to contraindication to CT intravenous contrast, a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of CT component of a positron emission tomography (PET)-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically-based mRECIST 1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET-CT can be used for mRECIST1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an Investigator if it is not routinely or serially performed.

Bone scan or PET scan is not adequate for assessment of mRECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

MRI of brain without and with contrast should be acquired as outlined in Section 1.2 (Schedule of Events). CT of the brain without and with contrast can be performed if MRI is contraindicated.

Bone scans may be collected per local standards, as clinically indicated. Digital photography should be performed and submitted, if clinically indicated.

7.3 Imaging and Clinical Assessment

Tumor assessments should continue even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same Investigator using mRECIST 1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the electronic CRF (eCRF) based on the Investigator's assessment using mRECIST 1.1 criteria (See Appendix 9 for specifics of mRECIST 1.1 criteria to be utilized in this study). Assessments of PR and CR are recommended to be confirmed at least 4 weeks (28 days) after initial response. A Best Overall Response of SD requires a minimum of 56 days on study from randomization to the date of the first imaging assessment.

All patients must have measurable disease to be eligible for this study. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the 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 (Eisenhauer, 2009).

7.4 Central Imaging

Sites should submit all scans to the imaging core lab on the schedule outlined in the Study 17-214-09/CA045002 Imaging Manual, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and Investigator assessment of submitted scans. Clinical information (palliative radiotherapy on-study, surgical excision of any lesion, details of paracentesis and thoracocentesis) must be provided to the BICR team. All details on the timelines and associated process requirements will be outlined in the Imaging Manual.

All study treatment decisions will be based on the Investigator's assessment of tumor images and not on the BICR assessment. The BICR assessment of progression is only relevant for determining when tumor assessments for a given patient are no longer required to be submitted to the imaging vendor.

7.5 Additional Imaging Assessments for the Study

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) should be collected for mRECIST 1.1 tumor assessment and submitted to the BICR.

7.6 Patient-Reported Outcomes

The evaluation of patient-reported outcomes is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the patient's perspective and offer insights into patient experience that may not be captured through physician reporting. Additionally, generic health-related quality of life measures provide data needed for calculating utility values to inform health economic models.

Patients will be asked to complete the NCCN/FACT Symptom Index for Kidney Cancer (FKSI-19), EQ-5D-3L, and selected items from the Patient-Reported Outcomes version of the Common Term Criteria for Adverse Events (PRO-CTCAE). Patients will complete the patient-reported outcome measures as outlined in the schedules of events: Table 1 provides information regarding the timing of patient-reported outcomes assessments during the Screening period. Table 2 and Table 3 provide information regarding the timing of patient-reported outcomes assessments during the on-treatment period for Arms A and B, respectively. Table 4 provides information regarding the timing of patient-reported outcomes assessments during the follow-up period.

7.6.1 FKSI-19

The National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy–Kidney Symptom Index-19 (FKSI-19) is a 19-item self-reported questionnaire with a total score and four subscales that assess disease-related symptoms (DRS), treatment side effects (TSE), and function/well-being associated with advanced kidney cancer. It captures symptom severity and interference in activity and general health perceptions. The FKSI-19 comprises four subscales (DRS-Physical, DRS-Emotional, TSE, and Function/Well-Being). Each of the items is scored on a five-point scale from zero (not at all) to four (very much). Higher FKSI-19 scores indicate improvement (Rothrock, 2013).

The FKSI-19 uses a recall period of "the past 7 days."

7.6.2 EQ-5D-3L

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

Empirically-derived weights can be applied to an individual's responses to the EQ-5D-3L descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for the UK, US, Spain,

Germany, and numerous other populations. Utility index values range from a 1 (full health) to 0 (dead) with negative values indicating a state considered worse than being dead. In addition, the EQ-5D-3L includes a visual analog scale that allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health.

The EQ-5D-3L uses a recall period of "today."

7.6.3 PRO-CTCAE

The PRO-CTCAE is a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients participating in oncology clinical trials. It was designed to be used as a companion to the CTCAE, the standard lexicon for adverse event reporting in cancer trials. PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials. Selected items from the PRO-CTCAE will be administered. Patients will complete the PRO-CTCAE patient to the availability of language translations (Basch, 2014).

The PRO-CTCAE uses a recall period of "the last 7 days."

8.0 ASSESSMENT OF SAFETY

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

8.2 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 (see Section 8.7).

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.

8.3 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 (NCI) Common Terminology Criteria for Adverse Events (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 [e.g., insomnia, mild headache]).
- Grade 2 = Moderate (event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment [e.g., fever requiring antipyretic medication]).
- Grade 3 = Severe (event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention).
- Grade 4 = Life threatening or disabling.
- Grade 5 = Death.

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

8.4 Causality Relationship of AEs

The relationship of each AE to each study drug (NKTR-214 and/or nivolumab, sunitinib or cabozantinib) 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. 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.

8.5 AE Reporting and Follow-up

After initiation of study drug treatment, all AEs except for SAEs (Section 8.7 and 8.8) will be reported from the time of first study drug(s) administration until 100 days after the last dose of all study drug(s) (see Section 5.6).

All ongoing non-serious AEs will be followed until resolution, the patient is lost to follow-up, patient death, or until the last Safety Follow-Up Visit. If the AE has not completely resolved by the last Safety Follow-Up 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 8.6 and 8.7.

8.6 Serious AE Definition

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

- Results in death.
- Is life threatening, i.e., in the opinion of the Investigator, the AE places the patient at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization that occurs during the course of a patient's participation in a clinical study, except for those due to the following:
    - A surgery or procedure that was planned before the patient entered the study and which is part of the planned study procedure.
    - Nonmedical reasons (e.g., elective hospitalization 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 8.9). 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.

8.7 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. Any new or clinically significant changes in the patient's medical and/or cancer history that occur after the first dose of drug and meet the SAE criteria will be recorded as SAEs. All SAEs, regardless of causality or starting subsequent anticancer therapy, with an onset within 100 days after the last dose of all study drug(s) will be reported to Nektar Therapeutics Drug Safety immediately (i.e., no more than 24 hours after learning of the event).

In addition, all SAEs that occur beyond 100 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 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 within 24 hours of awareness. A follow-up SAE report and any additional records (including but not limited to, hospital records, consultant reports, autopsy findings, and records needed to address queries sent from Sponsor) will be emailed or faxed to Nektar Therapeutics Drug Safety within 24 hours of awareness. Any medication or other therapeutic measures used to treat the event will be recorded.

All SAEs will be followed as described in Section 8.8.

Reporting of SAEs to the IRB/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.

8.8 Serious AE Follow-up

All study treatment-related SAEs that have not resolved by the last Safety Follow-Up visit (Section 5.6) will be followed until any of the following occur (whichever comes first):

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

All ongoing SAEs assessed as unrelated to study drug(s) will be followed until resolution or until the last Safety Follow-Up Visit (Section 5.6.1), whichever is earlier. In the case where an unrelated SAE has not completely resolved by the last Safety Follow-Up Visit, the final outcome of these ongoing unrelated SAEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

8.9 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 (e.g., pleural effusion) that meet "seriousness" criteria (e.g., hospitalization). These 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.

8.10 Immune-mediated Adverse Events 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 (e.g., 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. Information supporting the assessment of imAEs will be collected on the case report form.

Additional information may also be collected on select AEs primarily related to NKTR-214, including cytokine release syndrome and capillary leak syndrome.

8.11 Adverse Events of Special Interest

The AEs listed below are considered AESIs. 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 as described in Section 8.7) from the sites to Nektar Drug Safety: pharmacovigilance@nektar.com.

- CVA events (including TIA; any grade; CVA Management Guidelines are provided in Appendix 6)

8.12 Pregnancy Tests/Pregnancy

8.12.1 Pregnancy Tests

Serum or urine pregnancy tests will be performed on WOCBP during screening. Serum or urine pregnancy tests will be performed by a local laboratory on women within 24 hours of Day 1 of each cycle prior to dosing. Urine pregnancy tests should have a minimum sensitivity of 25 IU/L or equivalent units of hCG. 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 (see Appendix 4) for at least 1 year or surgically sterile for at least 3 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 8.12.2.

8.12.2 Pregnancy

8.12.2.1 Pregnancies in Female Patients

The Sponsor must be notified immediately without undue delay, under no circumstances later than 24 hours following knowledge of the initial report and any follow-up reports of a female patient becoming pregnant during the course of the study and for 5 months post treatment

completion for female patients. All reports should be submitted via the Pregnancy Notification Form. Pregnancy, although reportable, is not considered an AE/SAE unless a female patient 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 8.7. Female patient(s) who become pregnant will be followed until the outcome of the pregnancy is known. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring.

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

8.12.2.2 Pregnancies in Female Partners of Male Patients

Any pregnancy occurring during the course of the study and for 3 months after the last dose of NKTR-214 in a female partner of a male patient must be reported to the Sponsor. The Sponsor must be notified immediately without undue delay, under no circumstances later than 24 hours following knowledge of the initial report and any follow-up information. All reports should be submitted via the Pregnancy Notification Form. In order for the Sponsor or designee to collect any pregnancy surveillance information, the pregnant patient or partner must sign an informed consent form (See Section 12.2).

Pregnancy, although reportable, is not considered an AE/SAE unless a female partner of male patient 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 8.7. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug with the authorization from the pregnant partner. 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.

8.13 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 8.7 for reporting details).

Potential DILI 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.

8.14 Emergency Medical Support and Patient Card

Patients enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor. The Emergency Medical Support card is based on the need to provide clinical trial patients with a way of identifying themselves as participating in a clinical trial, and subsequently to give health-care providers access to the information about this participation that may be needed to determine the course of the patient's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial. Clinical trial Investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their patients.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected patient. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, he/she will answer any questions. Any subsequent action will follow the standard processes established for the Investigators. In cases where the Investigator is not available, the Sponsor will provide a 24-hour contact number, whereby health care providers are given access to a physician designated by the Sponsor who can assist with the medical emergency.

8.15 Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Events (Section 1.2). Clinical laboratory tests will be performed by the central laboratory. In addition, local laboratory testing within 24 hours, or as soon as locally feasible, is required prior to each study drug administration or dispensation or as clinically indicated. A list of the clinical laboratory analytes to be tested is provided in Appendix 3. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. Laboratory samples may be split (or 2 sets of samples collected) to allow a local laboratory analysis in addition to the central laboratory. Eligibility will be based on central laboratory results. However, for randomization, if the central laboratory tests are cancelled, lost, or considered inadequate for analysis, the site may forward local laboratory results for eligibility review and IMDC score calculation (with central laboratory testing repeated prior to the first dose of study drug). If local

laboratory results are determined to be acceptable during eligibility review, randomization may proceed. During the Treatment Period, treatment decisions and assessment of adverse events may be based on local laboratory test data (see Appendix 3 for details on minimum required local laboratory tests for scheduled treatment visits), although central lab sample collection still applies. The Investigator or qualified Sub-Investigator will review clinical laboratory test data, including at minimum Screening central laboratory data and both local and central laboratory results for all post-randomization assessments. Additional clinical laboratory tests may be ordered at the Investigator's or qualified Sub-Investigator's discretion.

The Investigator or qualified Sub-Investigator will review all laboratory results (both local and central) for clinical significance. Any laboratory result deemed clinically significant (i.e., is associated with signs and symptoms, requires treatment, or requires follow up) will be recorded as an AE as described in Section 8.1.

8.16 Physical Examinations

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

8.17 Vital Signs

Vital sign measurements will be recorded according to the Schedule of Events (Section 1.2). Vital signs include heart rate, systolic and diastolic blood pressure, and temperature. It is preferred that the same arm be used for all blood pressure readings, if possible. Pulse oximetry will also be included during Screening and as clinically indicated. Weight is to be reported at each vital sign visit, height at screening visit only.

8.18 Electrocardiograms

All patients will have 12-lead electrocardiogram (ECG) done during Screening as specified in the Schedule of Events. After randomization, patients with clinically significant cardiac toxicity should have this assessment repeated as indicated. For patients receiving sunitinib or cabozantinib, periodic monitoring with on-treatment electrocardiograms should be considered per its product labeling information.

8.19 Echocardiograms

Standard echocardiogram will be performed at screening to assess cardiac function and LVEF according to the Schedule of Events. A MUGA scan can be performed to assess cardiac function

and LVEF if a standard echocardiogram cannot be performed. After randomization, patients with clinically significant cardiac toxicity should have this assessment repeated as indicated.

9.0 STATISTICAL PLAN

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 treatment arm.

The efficacy endpoints will be analyzed using the IMDC intermediate- or poor-risk population, and IMDC all-risk population. All safety endpoints will be summarized using the Safety Population.

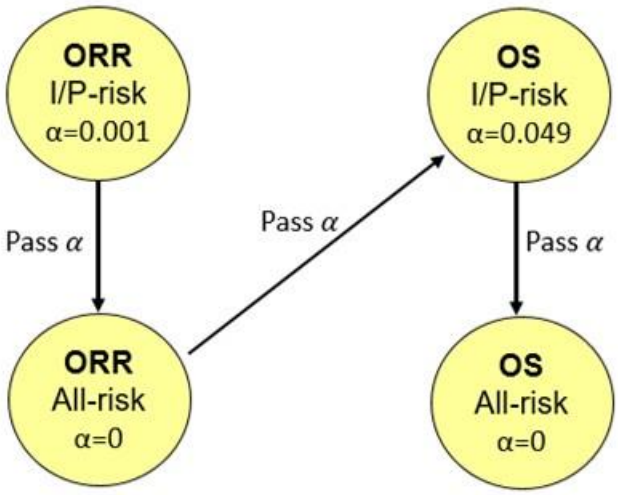
A detailed description of analysis methods will be provided in the statistical analysis plan (SAP).

9.2 Determination of Sample Size

The sample size of the study accounts for the following primary efficacy endpoints: ORR in IMDC intermediate- or poor-risk and IMDC all-risk populations, and OS in IMDC intermediate- or poor-risk and IMDC all-risk populations. The overall alpha for this study is 0.05, which is split with 0.001 to evaluate ORR and 0.049 to evaluate OS. All alpha levels are two-sided. The test in IMDC all-risk population is gated by the one in IMDC intermediate- or poor-risk population for both ORR and OS. That is, ORR in IMDC all-risk population will not be tested unless ORR in IMDC intermediate- or poor-risk population is statistically significant; and similarly, OS in IMDC all-risk population will not be tested unless OS in IMDC intermediate- or poor-risk population is statistically significant.

In addition, a fallback approach will be used to reallocate alpha from ORR to OS. If ORR is significant in IMDC intermediate- or poor-risk and IMDC all-risk populations, the alpha of 0.001 will be passed to OS. OS in IMDC intermediate- or poor-risk population can then be tested at 0.05 (instead of 0.049) level. If it is significant, the alpha of 0.05 will be passed to OS in IMDC all-risk population. The testing procedure of ORR and OS is described in Figure 2. The total planned sample size is 600 patients. It is estimated that at least 500 IMDC intermediate- or poor-risk and approximately 100 IMDC favorable-risk, previously untreated advanced RCC patients will be randomized into the two treatment arms (NKTR-214 combined with nivolumab vs TKIs) in a 1:1 ratio.

Figure 2: Statistical Testing Procedure



9.2.1 Sample Size Justification for ORR

Given a two-sided alpha of 0.001, 500 patients in the IMDC intermediate- or poor-risk population will provide approximately 82% power to detect an 18% difference in ORR between the 2 treatment arms using a Chi-square test, assuming an ORR of 27% for TKIs. If the observed ORR difference is greater than 13.9%, the result will be statistically significant. Six hundred patients in the IMDC all-risk population will provide approximately 89% power to detect an 18% difference in ORR between 2 treatment arms using a Chi-square test, assuming an ORR of 32% for TKIs. If the observed ORR difference is greater than 13.2%, the result will be statistically significant. If ORR is significant in IMDC intermediate- or poor-risk population, the alpha of 0.001 will be passed to ORR in IMDC all-risk population.

This ORR analysis will occur at the time of the interim analysis of OS. Based on the average accrual rate of 28 patients per month, at the time of OS interim analysis, it is estimated that 600 patients in the IMDC all-risk population would have been enrolled and followed for 6 months of which at least 500 patients will be IMDC intermediate- or poor-risk.

9.2.2 Sample Size Justification for OS

The study is powered to detect an improvement in OS for NKTR-214 combined with nivolumab as compared to TKIs. Due to the long duration of OS and potential subsequent non-protocol therapies, there may be confounding issues for the OS endpoint. Thus, it is critically important to use interim OS results to efficiently power the OS endpoint and conduct the final analysis as early as possible using an adaptive approach. The interim analysis will be triggered when at least 156 OS events in IMDC intermediate- or poor-risk population are observed. All primary endpoints will be tested at this interim analysis. Two parallel sequential tests will be conducted: (1) ORR in IMDC intermediate- or poor-risk and IMDC all-risk populations at $\alpha = 0.001$ and (2) OS in IMDC intermediate- or poor-risk and IMDC all-risk populations at $\alpha = 0.01$. Within (1),

ORR in IMDC all-risk population will only be tested at 0.001 if ORR in IMDC intermediate- or poor-risk is statistically significant at 0.001. Within (2), OS in IMDC all-risk population will only be tested at 0.01 if OS in IMDC intermediate- or poor-risk is statistically significant at 0.01.

The overall Type I error rate is 0.05 for the primary OS analysis in IMDC intermediate- or poor-risk and IMDC all-risk populations assuming ORR is significant in both IMDC intermediate- or poor-risk and IMDC all-risk populations. The alpha of 0.01 will be spent at interim and the remaining alpha of 0.04 will be spent at final analysis corresponding to the statistical significance level of 0.047 calculated based on the correlation of the interim and final CHW test statistic. If ORR is not statistically significant in either population, an overall alpha of 0.049 will be used for OS where 0.01 will be spent at interim and the remaining alpha of 0.039 will be spent at final analysis corresponding to the statistical significance level of 0.046. The detailed calculation is provided in the SAP.

If OS in the IMDC intermediate-or poor-risk population is not statistically significant, conditional power will be calculated based on this population. The adaptive method in Liu and Hu (2016), and Mehta and Pocock (2011) will be used to determine the number of OS events in IMDC intermediate- or poor-risk population needed to target approximately 85% to 90% conditional power for the final analysis. The final analysis will be triggered when this re-estimated number of OS events in IMDC intermediate- or poor-risk is reached. The test of OS in IMDC all-risk population will be also performed at this time regardless of number of events observed in this group.

If OS in the IMDC intermediate- or poor-risk population is statistically significant, but not in the IMDC all-risk population, then the conditional power will be calculated for the IMDC all-risk population. The adaptive method in Liu and Hu (2016), and Mehta and Pocock (2011) will be used to determine the number of OS events in IMDC all-risk population needed to target approximately 85% to 90% conditional power for the final analysis.

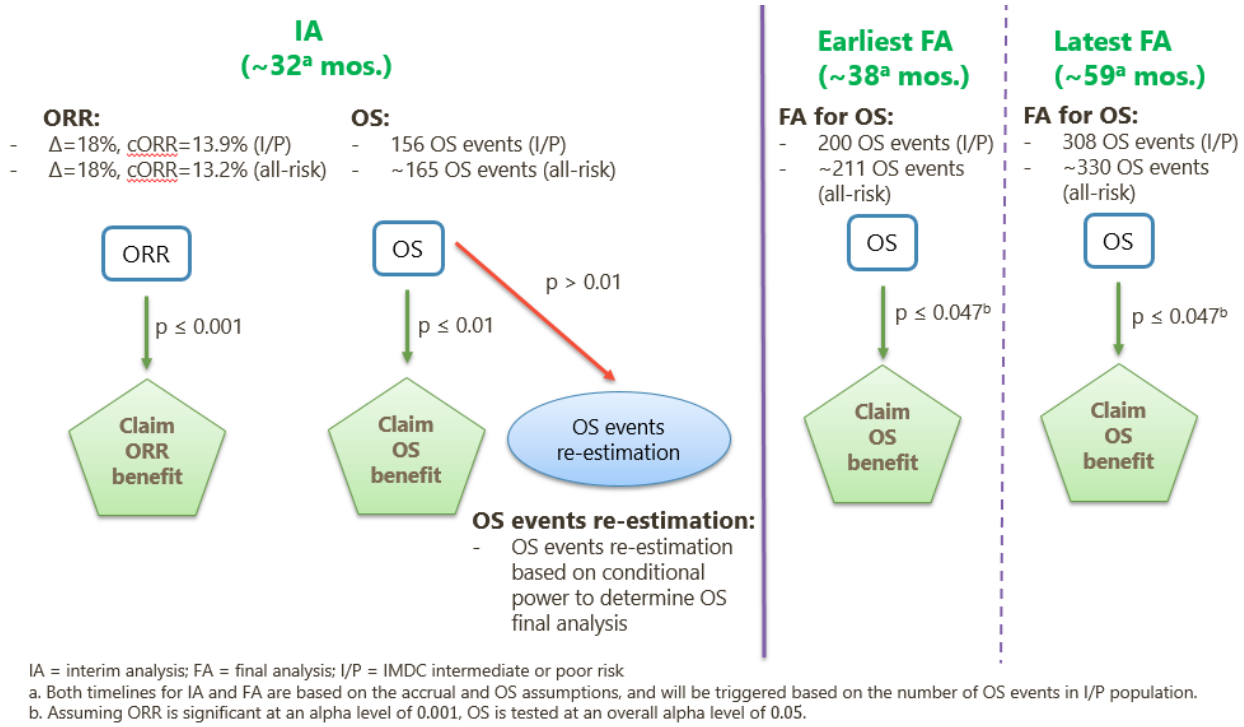
The minimum and maximum number of OS events in IMDC intermediate- or poor-risk population for the final analysis are 200 and 308, respectively. The minimum event size is calculated to achieve 90% power with alpha = 0.049 (two-sided) assuming an exponential distribution in each treatment arm and a HR = 0.63 with median OS for the TKI arm of 26 months in IMDC intermediate-or poor-risk population. The maximum event size is determined based on the minimum clinically meaningful effect.

The detailed sample size adaptation rules based on conditional power will be described in an appendix of the Data Monitoring Committee (DMC) Charter, which will not be accessible to the study team or sites to prevent introduction of any potential bias; however, the operational procedures will be described in the DMC charter, which is accessible to the study team.

The key secondary endpoint of PFS in IMDC intermediate- or poor-risk population and IMDC all-risk population will be tested hierarchically given statistical significance of OS. Further details of the testing procedure will be described in the SAP.

Figure 3 provides the study flow and decision-making time points for the primary endpoints.

Figure 3: Study Flow and Decision-Making Time Points



IA = interim analysis; FA = final analysis; I/P = IMDC intermediate or poor risk
a. Both timelines for IA and FA are based on the accrual and OS assumptions, and will be triggered based on the number of OS events in I/P population.
b. Assuming ORR is significant at an alpha level of 0.001, OS is tested at an overall alpha level of 0.05.

9.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
Intent-to-Treat (ITT) IMDC Intermediate- or Poor-risk Population	All patients who are randomized and are classified as the intermediate- or poor-risk according to the IMDC prognostic score. Patients are grouped by the treatment to which they were randomized.
Intent-to-Treat IMDC All-risk Population	All patients who are randomized. Patients are grouped by the treatment to which they were randomized.
Safety IMDC Intermediate- or Poor-risk Population	All patients who receive at least 1 dose (or partial dose) of study drug and are classified as the intermediate- or poor-risk according to the IMDC prognostic score. Patients are grouped according to the treatment they actually received.
Safety IMDC All-risk Population	All patients who receive at least 1 dose (or partial dose) of study drug. Patients are grouped according to the treatment they actually received.
ORR IMDC Intermediate- or Poor-risk Population	All randomized patients classified as the intermediate- or poor-risk according to the IMDC prognostic score who have at least 6 months of follow-up at the time point of the ORR analysis. A patient's follow-up time is defined here as the time between randomization date and clinical data cut-off date regardless of patient disposition (i.e., ITT principle). Patients are grouped by the treatment to which they were randomized
ORR IMDC All-risk Population	All randomized patients who have at least 6 months of follow-up at the time point of the ORR analysis. A patient's follow-up time is defined here as the time between randomization date and clinical data cut-off date regardless of patient disposition (i.e., ITT principle). Patients are grouped by the treatment to which they were randomized.
Pharmacokinetic Population	All patients in the Safety Population who have evaluable analysis concentration-time profiles that allow for computation of meaningful PK parameter values

9.4 Demographics and Baseline Characteristics

A descriptive summary of demographics and key baseline characteristics will be provided. Details will be included in the SAP.

9.5 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	
ORR by BICR in IMDC intermediate- or poor-risk population and IMDC all-risk population	ORR is defined as the percentage of patients with a confirmed best overall response of CR or PR by mRECIST 1.1 per BICR. The primary ORR analysis will be performed on the ORR population using treatment group "as randomized." The ORR will be compared using a Cochran-Mantel Haenszel (CMH) test stratified by the two stratification factors (IMDC prognostic score and TKI choice) at a 0.001 alpha level. The ORR difference between the two treatment arms with its 95% and 99.9% confidence interval (CI) will be reported. The ORR and its corresponding 95% exact CI will also be calculated by Clopper-Pearson method for each arm. Patients who do not have sufficient baseline or on-study tumor assessments to evaluate response status will be counted as failures. A fallback approach will be used to test ORR and OS. If ORR is significant in IMDC intermediate- or poor-risk and IMDC all-risk populations, the alpha of 0.001 will be passed to OS. OS in IMDC intermediate- or poor-risk population can then be tested at 0.05 (instead of 0.049) level. If it is significant, the alpha of 0.05 will be passed to OS in IMDC all-risk population.
OS in IMDC intermediate- or poor-risk population and IMDC all-risk population	Overall survival (OS) is defined as the time between the date of randomization and the date of death due to any cause. 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. The OS analysis will use the IMDC intermediate or poor risk and IMDC all-risk subsets of the ITT population. The overall Type I error rate is 0.05 for the primary OS analysis in IMDC intermediate- or poor-risk and IMDC all-risk populations assuming ORR is significant in both IMDC intermediate- or poor-risk and IMDC all-risk populations. The alpha of 0.01 will be spent at interim and the remaining alpha of 0.04 will be spent at final analysis corresponding to the statistical significance level of 0.047 calculated based on the correlation of the interim and final CHW test statistic. If ORR is not statistically significant in either population, an overall alpha of 0.049 will be used for OS where 0.01 will be spent at interim and the remaining alpha of 0.039 will be spent at final analysis corresponding to the statistical significance level of 0.046. Within each analysis, OS in IMDC intermediate- or poor-risk population will be tested first, and only when it is statistically significant, OS in IMDC all-risk population can be tested at the same level. At the final analysis, the primary analysis of OS to claim statistical significance will be based on the CHW version of the stratified log-rank test statistic with pre-specified weights of $\sqrt{2/3}$ and $\sqrt{1/3}$ (Cui Hung Wang, 1999). Statistical significance level of 0.047 and 0.046 depending on the statistical significance of ORR is calculated based on the correlation between the interim and final CHW test statistics. The conventional stratified log-rank test with equal weights for every patient will be conducted as a sensitivity analysis. Details will be provided in the SAP. A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the hazard ratio and corresponding 95% CI. The Kaplan-Meier method will be used to further summarize OS, including Kaplan-Meier curves, and medians with corresponding 95% CIs. The OS rates at 12 and 24 months will also be estimated.
Key Secondary	
PFS by BICR in IMDC intermediate- or poor-risk population and	Progression-free survival is defined as the time between the date of randomization and the first date of documented tumor progression using mRECIST 1.1 per BICR or death due to any cause, whichever comes first. Due to the delayed effect observed for PFS in the Checkmate-214 study (Motzer 2018b), the Fleming-Harrington weighted log-rank test (Harrington and Fleming 1982) will be used to test PFS in IMDC intermediate- or poor-risk

Endpoint	Statistical Analysis Methods
IMDC all-risk population	and IMDC all-risk populations. The Kaplan-Meier method will be used to summarize PFS, similar to OS. Patients who do not progress or die will be censored on the date of their last evaluable tumor assessment. Patients who do not have any on-study tumor assessments and do not die will be censored on their date of randomization. Patients who started a subsequent anticancer therapy prior to disease progression will be censored on the date of their last evaluable tumor assessment prior to receiving the subsequent anticancer therapy. Patients who are lost to follow up will be censored on the date of their last evaluable tumor assessment. PFS per Investigator assessment will also be performed. Details and additional sensitivity analyses will be described in the SAP.
Other Secondary	
Duration of Response	Duration of response (DOR) is defined for patients who have a confirmed CR or PR as the date from first documented CR or PR per mRECIST 1.1 to the date of the documentation of disease progression as assessed by BICR or death due to any cause, whichever is earlier. The same censoring method used for the primary PFS analysis will be applied. The median DOR will be estimated using the Kaplan-Meier method with corresponding 95% CI and range. The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented. Time to response (TTR) is defined for patients who had a confirmed CR or PR as the time from the date of randomization to date of first documented CR or PR per mRECIST 1.1 as assessed by BICR. The median TTR will be estimated using the Kaplan-Meier method with corresponding 95% CI and range. The clinical benefit rate (CBR), defined as the number of patients with CR, PR, or SD per mRECIST 1.1 by BICR, will be summarized similarly to ORR. Note that a best overall response of SD requires a minimum of 56 days on study from randomization to date of the first tumor assessment. ORR, DOR, TTR, and CBR assessed by Investigator per mRECIST 1.1 will be analyzed similarly to these endpoints assessed by BICR. ORR, DOR, TTR, and CBR assessed by Investigator per mRECIST 1.1 will be analyzed similarly to these endpoints assessed by BICR.
PFS2	PFS after the next line of treatment (PFS2) is defined as time from randomization to progression per Investigator after the start of next line of therapy or death, whichever occurs first. Patients who were alive and without progression after the next line of therapy will be censored at their last known alive date. Details on PFS2 analysis will be described in the SAP.
FKSI-19	Summary statistics for FKSI-19 score (and its 4 subscales) at each assessment point will be summarized for each treatment group. The mean change from baseline will also be reported at each post baseline assessment point.
EQ-5D-3L	Summary statistics for EQ-5D-3L (5 dimensions) at each assessment point will be summarized for each treatment group. The mean change from baseline will also be reported at each post baseline assessment point.
PRO-CTCAE	Summary statistics for PRO-CTCAE at each assessment point and per item will be summarized for each treatment group. The mean change from baseline will also be reported at each post baseline assessment point.
HCRU	Summary statistics for HCRU at each assessment point will be summarized for each treatment group.

9.6 Safety Analyses

Endpoint	Statistical Analysis Methods
Other Secondary	Safety analyses will be performed in all treated patients. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 5.0 criteria by system organ class and preferred term. On study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 5.0 criteria.

9.7 Interim and Final Analyses

- Interim Analysis (ORR & OS interim and OS events re-estimation): when at least 156 OS events in IMDC intermediate- or poor-risk population have been observed.
- Final Analysis (OS final): timing will be determined based on the Interim Analysis efficacy results.

The SAP will further describe the planned interim analyses.

[redacted]

9.9 Data Monitoring Committee

When required, adjudicated events will be submitted to a DMC and Health Authorities for review. The DMC will be comprised of qualified clinicians and a biostatistician, all independent from the Sponsor and investigational sites, selected to avoid conflict(s) of interest. The DMC will review the results of the interim analyses as well as assess accumulating safety data and emerging risk/benefit balance at regular intervals and on an ad-hoc basis as detailed in the DMC charter. The DMC will also conduct the OS events re-estimation; details will be provided in the DMC charter.

The DMC's specific activities will be detailed in a mutually agreed upon charter, which will define the relevant processes, including meeting proceedings and structure, data assessments, documentation and recordkeeping, process for DMC recommendations, and regulatory reporting, as applicable. The charter will contain procedures to ensure the minimization of bias, such as maintaining confidentiality of any interim data.

10.0 STUDY OR STUDY SITE TERMINATION

The Sponsor has the right to suspend or terminate the study. Sponsor reasons for suspension or termination of the study may include, but are not limited to the following:

- Study is terminated due to safety concerns (i.e., the benefit-risk balance is unacceptable)
- Lack of efficacy or not meeting the study objectives
- Development of NKTR-214 is terminated

If an Investigator suspends or terminates their study site, the Investigator will promptly (if possible, within 24 hours) 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, summaries, and other documentation as required by health authorities, IRB/IEC, and other regulatory requirements.

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/IEC and the regulatory agency, as required by regulations, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve only logistical or administrative aspects of the study. Any deviation may result in the patient having to be withdrawn from the study and rendering that patient nonevaluable. All protocol deviations and the reasons for such deviations are to be documented and reported to the Sponsor promptly.

11.2 Monitoring

In accordance with Code of Federal Regulations 21 CFR 312.56, International Council for Harmonisation (ICH) GCP, and local regulations, the clinical monitor will periodically inspect all 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, 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 (IND) Application regulations and ICH GCP 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

The Sponsor or designees may conduct 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 shall 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 ETHICAL CONSIDERATIONS

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 ICH GCP, 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, Investigator's Brochure, and ICF will be reviewed and approved by the applicable regulatory authority and/or competent IRB/IEC. A letter documenting the IRB/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 in accordance with Section 11.1.

The Investigator, Sponsor, or their designees will submit a progress report at least once yearly to the IRB/IEC, or more frequently if required by the IRB/IEC. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB/IEC per the IRB/IEC requirements, and in compliance with FDA regulations, applicable regulatory authority requirements, and ICH GCP.

The Investigator, the Sponsor, or their designees shall promptly notify the IRB/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/IEC local requirements, and in compliance with FDA regulations, regulatory authority regulations, and ICH GCP.

12.2 Written Informed Consent

A freely and voluntarily written documentation of informed consent must be obtained from each patient or if the patient is an incapacitated person or a minor their legal representative before entering the study. The content and approval of the ICF must meet requirements of regulations and ICH GCP. Patients will be informed of all aspects of the study that are relevant to the patient's decision to participate, 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.

Any pregnancy that occurs in a study patient or the female partner of a male study patient should be reported to the Sponsor or designee. Only if a pregnant patient or partner has signed an informed consent form for disclosure information will the Sponsor or designee be able to collect

any pregnancy surveillance information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form (see Section 8.12.2).

13.0 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection Instruments and Source Documents

13.1.1 Study Records

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

13.1.2 Data Collection Instruments

Data collection instruments (DCIs) (e.g., eCRFs, electronic clinical outcomes assessments [eCOAs], 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

The Essential Documents contained in the clinical trial master files shall be retained for 25 years or per local and regional regulations and guidelines, whichever is longer. These documents should be retained for a longer period, however, if required by an agreement with the Sponsor. At all times, the retention must meet applicable data protection laws. It is the responsibility of the Sponsor to inform the Investigator/institution in writing as to when these documents no longer need to be retained.

The Investigator shall archive the clinical trial master file securely and in a way that ensures that it is readily available and accessible, upon request, to the regulatory authorities. Sites must inform the Sponsor in writing if documents will be disposed of per Institutional Policy.

The Investigator will contact the Sponsor before transferring or destroying any study records. The Investigator will also promptly notify the Sponsor in writing in the event of accidental loss or destruction of any study records.

13.3 Confidentiality

Patient confidentiality will be maintained per legal and regulatory requirements and ICH GCP. 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.

Study data given to, and used by, Nektar are protected by the use of a patient identification number. The assignment of unique patient identification number to each patient IRT system enables de-identification.

Demographic identifiers that will be collected as part of Study Data include year of birth, age, gender, race, and ethnicity provided this is permitted under applicable laws. Exact date of birth and patient name/initials are not collected.

The study site is not to attach the names or other directly identifying information of the patients to any Study Data or biological samples that will be transferred to Nektar. Only pseudonymized / key-coded Study Data and biological samples will be transferred to Nektar, and only the study site will be able to connect the patient identification number to a patient's personal data.

13.4 Security Measures

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

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

14.0 PUBLICATION PLAN

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).

Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement governing participation in the study. Study data shared by Nektar will not contain patient identifiable information.

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: INTERNATIONAL METASTATIC RCC DATABASE CONSORTIUM (IMDC) PROGNOSTIC CRITERIA

Adverse Prognostic Factors
Clinical
Karnofsky Performance Status < 80 Time from initial diagnosis to randomization < 1 year
Laboratory (central)[a]
Hemoglobin < LLN Corrected calcium > ULN [b, c] Absolute neutrophil count > ULN Platelet count > ULN

LLN = lower limit of normal; ULN = upper limit of normal

a. Based on most recent central laboratory results prior to randomization. If the central laboratory test results prior to randomization are unevaluable, the last local laboratory results prior to randomization may be used for eligibility review and IMDC score calculation (See Section 8.15).

b. Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL.

c. Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 (40 - serum albumin [g/L]), where 40 represents the average albumin level in g/L.

Risk Group Based on Number of Adverse Prognostic Factors	
Number of Adverse Prognostic Factors Present	**Risk Groups**
0	Favorable
1 – 2	Intermediate
3 – 6	Poor

Heng, 2009

APPENDIX 2: PERFORMANCE STATUS CRITERIA

Karnofsky Performance Status Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead

Schag, 1984

APPENDIX 3: CLINICAL LABORATORY TESTS

Local Clinical Laboratory Tests Obtained Prior to Study Drug Administration or Dispensation

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

WOCBP = women of child-bearing potential

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

Clinical Laboratory Test Panel

Hematology	Chemistry	Serology (screening only)
• Hemoglobin (Hgb) • Hematocrit (HCT) • Platelet count • White blood cell (WBC) count • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	• AST (SGOT) • ALT (SGPT) • Alkaline phosphatase (ALP) • Albumin • Creatinine • Calculated creatinine clearance • Calcium • Glucose (non-fasting) • Total protein (TP) • Total bilirubin • Sodium • Potassium • Chloride • CO_2 content or bicarbonate • Blood urea nitrogen (BUN) or serum urea • Lactate dehydrogenase (LDH) • Uric acid	• Hepatitis B surface antigen (HBsAg) • Hepatitis C virus antibody (anti-HCV) • Human immunodeficiency virus (HIV) antibody
Coagulation		**Additional Labs**
• Partial thromboplastin time (PTT) • Prothrombin time (PT)		• Creatine kinase • Serum or urine pregnancy (hCG) for WOCBP • FSH [a] • Thyroid stimulating hormone (TSH) • Free thyroxine (T4) • Free or total triiodothyronine (T3) • Lipase • Amylase • C-reactive protein (Screening only)

Urinalysis	
• Specific gravity • pH • Glucose • Protein • Bilirubin • Ketones • Leukocyte esterase • Blood • Creatinine	For positive protein, white blood cell or blood, a microscopic examination including: • Red blood cells • White blood cells • Epithelial cells • Bacteria • Crystals • Casts
For urine protein, UPCR is required at Screening, and if UPCR ≥ 1.0 [≥113 mg/mmol], measurement of 24-hour urine protein is required to confirm patient meets eligibility criteria (see Inclusion Criteria 9). Post-randomization, UPCR or dipstick analysis is acceptable; if UPCR ≥ 2.0 [≥ 227 mg/mmol] or dipstick protein ≥ 3+, measurement of 24-hour urine protein is required	

a. Post-menopausal females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause (see Appendix 4).

APPENDIX 4: WOMEN OF CHILDBEARING POTENTIAL, DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Women of Childbearing Potential (WOCBP)

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 WOCBP:

- 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 (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PATIENTS OF CHILDBEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end 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[b] • oral • intravaginal • transdermal

Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • oral • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • 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 WOCBP 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. • WOCBP patients who choose complete abstinence must continue to have pregnancy tests, as specified in Section 1.2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP patients chooses to forego complete abstinence
NOTES: 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. b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. c. Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable 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 • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

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 the end of relevant systemic exposure defined as 3 months after the last dose of NKTR-214.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 3 months after the last dose of NKTR-214 in the male patient.
- 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 3 months after the last dose of NKTR-214.
- Refrain from donating sperm for the duration of the study treatment and until 3 months after the last dose of NKTR-214.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information is provided in Section 8.12.2.

APPENDIX 5: CORTICOSTEROID DOSE EQUIVALENTS

Equivalent Dose	Steroid
1.2 mg	Betamethasone
1.5 mg	Dexamethasone
8 mg	Methylprednisolone
8 mg	Triamcinolone
10 mg	Prednisone
10 mg	Prednisolone
40 mg	Hydrocortisone
50 mg	Cortisone

Mager, 2003; Webb, 2005

APPENDIX 6: CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM (ARM A AND ARM B)

The table below provides a management algorithm for possible signs/symptoms of cerebrovascular accident (CVA) for patients in Arm A treated with the combination of NKTR-214 with a checkpoint inhibitor and patients in Arm B receiving sunitinib or cabozantinib. This general guideline constitutes guidance to the Investigator and may be supplemented by clinical judgment of the Investigator and/or discussions with the Medical Monitor representing the Sponsor.

For unexplained neurological symptoms (such as hemiparesis, confusion, dysarthria, or visual disturbances) that may be associated with CVA: • Recommend following the Advanced Cardiac Life Support (ACLS) Adult Suspected Stroke Algorithm that includes time-sensitive assessment and rtPA use guidance[a]. • Perform neurological imaging with DWI MRI as soon as feasible after the initial presentation of symptoms, preferably within 24 hours, or as indicated following an acute intervention. 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 event confirmed by imaging (DWI MRI preferred unless contraindicated), regardless of neurological symptoms (e.g., cryptogenic CVA), and for suspected TIA without clear alternative etiology: • Discontinue study treatment for patients in Arm A receiving NKTR-214 in combination with a checkpoint inhibitor (i.e., nivolumab) and patients in Arm B receiving sunitinib or cabozantinib.
2	Neurology consultation recommended.
3	Perform pertinent laboratory assessments including coagulation (D-dimer, complete blood count with differential, serum blood urea nitrogen, and creatinine) [redacted] preferably by central laboratory testing. Local laboratory testing is allowed when central laboratory testing is not possible.
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; rtPA = recombinant tissue plasminogen activator; TIA = transient ischemic attack.

a. ACLS-algorithms.com. Adult Stroke Algorithm, (ACLS) Advanced Cardiac Life Support [Internet]; 2021 [cited 5 May 2021]. Available from: https://acls-algorithms.com/adult-stroke-algorithm/.

APPENDIX 7: CYTOKINE RELEASE SYNDROME 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 cytokine release syndrome (CRS).

Cytokine Release Syndrome 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 (e.g., hydration management guidelines, Section 5.4.2.2).
- 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 (e.g., hydrocortisone 100 mg every 8 hours, dexamethasone 10 mg up to 4 times daily, methylprednisone 1-2 mg/kg/day IV or PO equivalent) • High-dose steroid (e.g., methylprednisolone 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	

Abbreviations: CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; ICU = intensive care unit; IV = intravenous; O_2 = oxygen; po = orally

APPENDIX 8: INDUCERS AND STRONG INHIBITORS OF CYP3A4

Inducers and Strong Inhibitors of CYP3A4[a]
CYP3A4 Inducers
Phenytoin
Carbamazepine
Rifampin
Rifabutin
Rifapentine
Phenobarbital
Dexamethasone
St. John's Wort
Strong CYP3A4 Inhibitors
Ketoconazole
Itraconazole
Posaconazole
Voriconazole
Clarithromycin
Erythromycin
Telithromycin
Nefazodone
Saquinavir
Lopinavir/ritonavir
Ritonavir
Atazanavir
Indinavir
Nelfinavir
Boceprevir
Conivaptan

Cabometyx, 2021; Sutent, 2019

a. Notes: Lists may not be exhaustive. Grapefruit, grapefruit juice and other foods that are known to inhibit CYP3A4 activity should be avoided during treatment. St. John's Wort (Hypericum perforatum) is known to be an inducer of CYP3A4 and should be avoided during treatment.

APPENDIX 9: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BRISTOL-MEYERS SQUIBB MODIFICATIONS

1. EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline with Bristol-Meyers Squibb modifications (Eisenhauer, 2009).

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

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/MRI scan (scan slice thickness no greater than 5 mm), or ≥ 2x slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. 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/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. 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.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal

disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone lesions

- Bone scan, positron emission tomography (PET) scan and plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4 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 two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

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.

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' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2. RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **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 diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum 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. (Note: the appearance of one or more new lesions is also 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.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor-quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet PD as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 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. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target Lesions that Become 'Too Small to Measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that Split or Coalesce on Treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the Patient Also has Measurable Disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. 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.

2.2.1.2 When the Patient Also has Non-Measurable Disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example,

necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of PD. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in PD.

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While fluorodeoxyglucose-positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 9 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 10 is to be used.

Table 9: Time Point Response: Patients With Target (± Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Table 10: Time Point Response: Patients with Non-Target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease

a. Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as

in Table 11. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the patient is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 56 days from the reference start date (reference date is considered Day 1 on study). If the patient is not on-study for at least this amount of time, any tumor assessment indicating SD before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 11: Best Overall Response (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 = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

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

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with unlimited intervening NEs (e.g., CR NE CR or CR NE NE CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (e.g., PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the patient is considered to not have PD.