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Nektar Therapeutics

CLINICAL STUDY PROTOCOL

Title:	A Phase 2, single-arm study of bempegaldesleukin (NKTR-214) in combination with nivolumab in cisplatin ineligible, locally advanced or metastatic urothelial cancer patients
Protocol Number:	18-214-10 / CA045-012
Protocol Amendment Number:	5.0
Protocol Amendment Date:	27 May 2021
Supersedes:	Amendment 4.0 dated 06 February 2020
US IND No.:	141226
Eudra CT No.:	2018-003636-79
Investigational Product:	bempegaldesleukin (NKTR-214)
Indication:	Locally advanced or metastatic urothelial bladder cancer
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA
Sponsor's Medical Contact and Study Medical Monitor:	[redacted]

CONFIDENTIALITY STATEMENT

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee and applicable Regulatory Authorities. Your acceptance of this document constitutes agreement that you will not disclose the information herein to others without written authorization from Nektar Therapeutics except to the extent necessary to obtain informed consent from persons who participate as patients in this study.

INVESTIGATOR SIGNATURE PAGE

Nektar Therapeutics

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PRINCIPAL INVESTIGATOR COMMITMENT

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

_____

Principal Investigator Signature

Printed Name:

Position:

PROTOCOL APPROVAL PAGE

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[redacted]
Signing Reason: I approve this document
Signing Time: Jun-02-2021 | 6:56:19 AM PDT
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Signature

[redacted]

LIST OF STUDY CONTACTS

Study Contact	Name	Contact Information
Nektar Medical Monitor	[redacted]	[redacted]
Serious AE and Pregnancy Reporting	[redacted]	[redacted]

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ABBREVIATIONS

Abbreviation or Term	Definition
1L	first line
AC	active cytokines
ACS	American Cancer Society
ADA	anti-drug antibodies
AE	adverse event
AEC	absolute eosinophil count
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the curve
bempegaldesleukin (bempeg, BEMPEG)	International Nonproprietary Name (INN) for NKTR-214
BP	blood pressure
BICR	blinded independent central review
BUN	blood urea nitrogen
C_{avgss}	steady state average concentration
CFR	Code of Federal Regulations
cHL	classical Hodgkin's lymphoma
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CMV	cytomegalovirus
CNS	central nervous system
CPI	checkpoint inhibitor
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRS	cytokine release syndrome

Abbreviation or Term	Definition
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated protein 4
CVA	cerebrovascular accident
DCI	data collection instrument
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOAC	direct oral anticoagulation
DOR	duration of response
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
EC_{50}	50% effective dose
ECG	electrocardiogram
ECHO	echocardiogram
ECLA	electrochemiluminescence assay
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EORTC	European Organization for the Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
EQ-5D-3L	EuroQol Group's EQ-5D questionnaire
ESMO	European Society for Medical Oncology
EU	European Union
FACIT GP5	Functional Assessment of Chronic Illness Therapy GP5 item
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GemCarbo	gemcitabine/carboplatin

Abbreviation or Term	Definition
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
high PD-L1	high programmed cell death ligand 1 (PD-L1) expression (i.e., Combined Positive Score [CPS] ≥ 10)
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HUS	hemolytic uremic syndrome
IC_{50}	50% inhibitory dose
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFNγ	interferon gamma
IHC	immunohistochemistry
IL	interleukin
IL-2	interleukin-2. *For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule.*
IL-2Rα	IL-2 receptor alpha subunit
IL-2Rαβγ	IL-2 receptor alpha beta gamma subunit
IL-2Rβγ	IL-2 receptor beta gamma subunit
imAE	immune-mediated adverse event
IMG	immunogenicity
IMP	investigational medicinal product
IND	Investigational New Drug application
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
kg	kilogram

Abbreviation or Term	Definition
KPS	Karnofsky performance status
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
low PD-L1	low programmed cell death ligand 1 (PD-L1) expression (i.e., Combined Positive Score [CPS] < 10)
LVEF	left ventricular ejection fraction
M-CAVI	methotrexate, carboplatin, and vincristine
MDSC	myeloid derived suppressor cells
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
min	minute(s)
mg	milligram
mL	milliliter
MLR	mixed lymphocyte reaction
mm Hg	millimeters of mercury
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mUC	metastatic urothelial carcinoma
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	natural killer
NKTR-214-AC	NKTR-214 active cytokines
NKTR-214-RC	NKTR-214 related cytokines
non-IMP	non-investigational medicinal product
non-IP	non-investigational product
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival

Abbreviation or Term	Definition
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PE	pulmonary embolism
PEG	polyethylene glycol
PFS	progression-free survival
PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
PSA	prostate-specific antigen
q14d	every 14 days
q2w	every 2 weeks
q3w	every 3 weeks
R	randomization
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
SCCHN	squamous cell carcinoma of the head and neck
[redacted]	[redacted]
SEC	Sponsor Executive Committee
SLD	sum of the longest diameters
SOP	standard operating procedure
SAR	serious adverse reaction
SARS-CoV-2; COVID-19	severe acute respiratory syndrome coronavirus 2
$t_{1/2}$	half-life
TCC	transitional cell carcinoma

Abbreviation or Term	Definition
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TIL	tumor infiltrating lymphocyte
T_{max}	time to maximum concentration
TMB	tumor mutation burden
TME	tumor microenvironment
Treg	regulatory T-cell
UBC	urothelial bladder cancer
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
V_d	volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential

1.0 STUDY SYNOPSIS

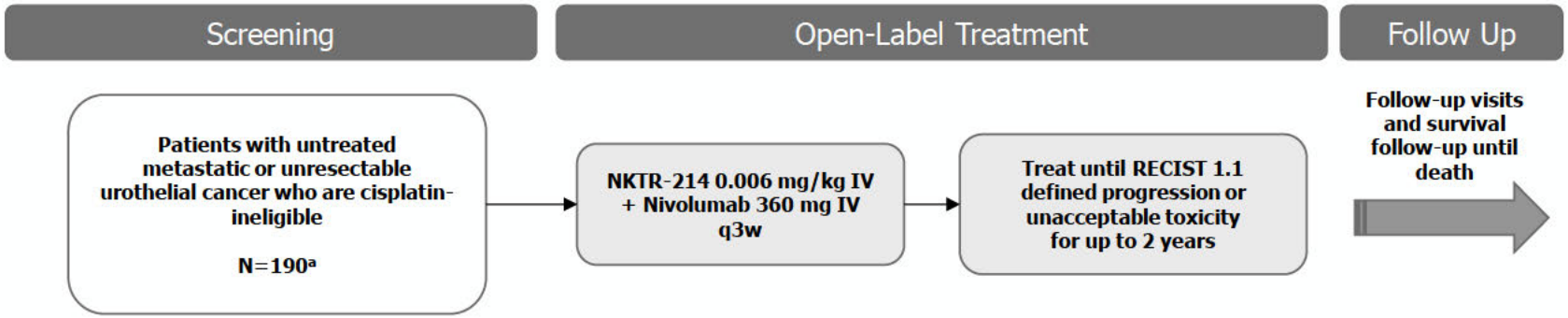
Title of Study:	A Phase 2, single-arm study of bempegaldesleukin (NKTR-214) in combination with nivolumab in cisplatin ineligible, locally advanced or metastatic urothelial cancer patients
Sponsor:	Nektar Therapeutics
Name of Finished Product(s):	Bempegaldesleukin (NKTR-214) Drug Product, Opdivo®
Name of Active Ingredient(s):	Bempegaldesleukin (NKTR-214) Drug Substance, nivolumab
Phase of Development:	2
Objectives:	The primary objective is: • To evaluate the anti-tumor activity of bempegaldesleukin (NKTR-214) in combination with nivolumab by assessing the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) per blinded independent central review (BICR) in patients whose tumors have low programmed cell death ligand 1 (PD-L1) expression The secondary objectives are: • To evaluate the effect of NKTR-214 in combination with nivolumab by assessing the ORR by RECIST 1.1 per BICR in all treated patients • To evaluate the effect of NKTR-214 in combination with nivolumab by assessing duration of response (DOR) by RECIST 1.1 per BICR in all treated patients and patients whose tumors have low PD-L1 expression • To evaluate the effect of NKTR-214 in combination with nivolumab by assessing the ORR and DOR by RECIST 1.1 per Investigator assessment in all treated patients and patients whose tumors have low PD-L1 expression • To evaluate the safety and tolerability of NKTR-214 in combination with nivolumab [redacted]

	
Duration of Treatment:	Patients will be treated until disease progression by RECIST 1.1 or loss of clinical benefit, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, patient decision to discontinue treatment or withdraw consent, loss to follow-up, Sponsor decision to terminate the study, or for a maximum of 2 years for patients receiving NKTR-214/nivolumab. Treatment duration for patients initially randomized to the gemcitabine/carboplatin (GemCarbo) arm is described in Section 4.1.6. Treatment may continue beyond progression if there is clinical benefit as determined by the Investigator.
Study Population:	Patients with locally advanced or metastatic urothelial cancer that are cisplatin ineligible and previously untreated.
Number of Patients (Planned):	The original protocol planned to enroll approximately 185 patients to receive NKTR-214 and nivolumab. Amendment 2.0 added a GemCarbo arm and reduced the overall number of patients planned to approximately 165 (110 to receive NKTR-214/nivolumab, 55 to receive GemCarbo). Amendment 3.0 eliminated the GemCarbo arm after 2 patients had enrolled in this arm, and modified the overall planned number of NKTR-214/nivolumab patients to 175. With Amendment 5.0, enrollment is complete at 2 patients who received GemCarbo and 190 patients who received NKTR-214/nivolumab.
Number of Study Sites:	Approximately 140
Countries:	Global
Study Design:	This is a Phase 2, single-arm study evaluating the safety and efficacy of NKTR-214 and nivolumab in cisplatin ineligible patients with locally advanced or metastatic urothelial cancer. Patients will be able to enroll regardless of their baseline PD-L1 expression, however, the study aims to enroll at least 110 patients whose tumors have low PD-L1 expression (defined as Combined Positive Score [CPS] < 10; referred to in this protocol as patients with low PD-L1) (Dako North America, Inc. 2018). Patients with CPS ≥ 10 will be considered to have high PD-L1 expression and will be referred to as high PD-L1 patients.
Key Eligibility Criteria:	• Male or female patients, age 18 years or older at the time of signing the informed consent form (ICF). • Patients must have histologically or cytologically documented inoperable, locally advanced (T4b, any N; or any T, N2-3) or metastatic (M1, Stage IV) urothelial cell carcinoma (also termed transitional cell carcinoma) including renal pelvis, ureters, urinary bladder and urethra.

	• Histologically or cytologically confirmed locally advanced and unresectable or metastatic urothelial cancer, including mixed urothelial cell and non-urothelial cell histologies. If the histology is mixed with non-urothelial carcinoma (e.g., squamous cell carcinoma), the urothelial cell component must be dominant (> 50% of the total histology). • Tumor tissue is required to be analyzed by the central laboratory to document PD-L1 status. Tissue can be provided in one of 2 ways: 1. A new biopsy taken during screening 2. Archival tissue from either a formalin fixed, paraffin embedded (FFPE) tissue block or unstained tumor tissue sections (see Section 7.5). Archival tissue must be within 12 months prior to enrollment and with no intervening treatment. A tracking number confirming shipment of the sample to the central laboratory must be supplied prior to Cycle 1 Day 1. • Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. • Patients must have measurable disease per RECIST 1.1 criteria, and have adequate organ function. • Patients must be able and willing to comply with the study visit schedule and study procedures. A patient will be excluded from this study if he/she has had prior systemic chemotherapy or an investigational agent for inoperable locally advanced or metastatic urothelial carcinoma before administration of first dose of study drug. Female patients who are pregnant or lactating, who plan to get pregnant, or who have a positive urine or serum pregnancy test are ineligible. All eligibility criteria are listed in Section 5.0.
Product, Dose and Mode of Administration:	NKTR-214 0.006 mg/kg intravenous (IV) every 3 weeks (q3w) with nivolumab 360 mg IV q3w, given on Day 1 of each 3-week cycle
Comparator Product, Dose and Mode of Administration:	Not applicable
[redacted]	[redacted]

Pharmacokinetic Evaluation:	Blood samples for PK will be collected from patients at multiple scheduled sampling times. Pharmacokinetic parameters such as maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the curve (AUC), clearance (CL), volume of distribution (V_d), and half-life ($t_{1/2}$) will be estimated from plasma or serum concentration-time data where possible.
Efficacy Evaluation:	Tumor measurements will be performed every 9 weeks ± 7 days. The primary endpoint is: • ORR by BICR in patients whose tumors have low PD-L1 expression The secondary endpoints are: • ORR per BICR in all treated patients • DOR by BICR in all treated patients and patients whose tumors have low PD-L1 expression • ORR and DOR by Investigator assessment in all treated patients and patients whose tumors have low PD-L1 expression All response and progression endpoints will be determined by BICR using RECIST 1.1. Patients will be assessed for response by computed tomography (CT) or magnetic resonance imaging (MRI) until progression or treatment discontinuation, whichever occurs later. After the first 12 months, tumor assessments will be done every 12 weeks (± 7 days). A scan should also be done at end of treatment (unless a scan was done within the prior 4 weeks). Patients who continue treatment beyond progression should continue to have scans every 9 weeks (± 7 days) for the first 12 months of treatment post-progression and every 12 weeks (± 7 days) in the second year of treatment post-progression. Tumor assessments in the follow-up period should be done every 90 days (± 10 days) from the last scan and are only needed if the patient discontinued treatment without radiographic disease progression.
Safety Evaluation:	Assessment of safety will be determined by an ongoing review of the following: • Adverse events, including incidence of treatment emergent AEs (TEAEs), incidence of treatment related AEs, serious AEs (SAEs), AEs leading to drug discontinuation • Clinical laboratory tests (blood and urine sampling) • Vital signs • Physical examination In addition to routine safety monitoring and pharmacovigilance activities, an Independent Data Monitoring Committee (IDMC) provided an initial safety review; subsequently a Sponsor Executive Committee (SEC) will provide formal safety reviews. The IDMC/SEC are described further in Section 10.11. Data from the first 20 patients who received at least 2 cycles of study treatment (6 weeks) with NKTR-214 and nivolumab were included in the initial planned safety review conducted by the IDMC.
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

	RECIST 1.1 per BICR. The ORR and its corresponding 95% exact confidence interval (CI) will be calculated by the Clopper-Pearson method. DOR is defined for patients who have a confirmed CR or PR as the date from first documented CR or PR per RECIST 1.1 to the date of documentation of disease progression as assessed by BICR or death due to any cause, whichever is earlier. Patients who do not have disease progression or die will be censored on the date of their last evaluable tumor assessment. The median DOR will be estimated using the Kaplan-Meier method with corresponding 95% CI and range. **Sample Size:** The total patient enrollment for this study is expected to be a maximum of 190 patients, including 2 patients who received GemCarbo under Amendment 2.0 of this protocol. (With Amendment 5.0, enrollment is complete at 2 patients who received GemCarbo and 190 patients who received NKTR-214/nivolumab). The study will evaluate the totality of the data including DOR, ORR, and CR rate. The number of patients to receive NKTR-214 and nivolumab was determined by the number of PD-L1 low patients expected to be present in an unselected population. Review of available urothelial carcinoma-specific PD-L1 data suggest that approximately 70% of patients have PD-L1 low tumors, while 30% have PD-L1 high tumors using the PD-L1 IHC 22C3 pharmDx assay (Vuky 2018; KEYTRUDA® Prescribing Information, 2018; TECENTRIQ® Prescribing Information, 2018). Utilizing this assumption, at least 110 enrolled patients are expected to have tumors that are PD-L1 low. The null hypothesis is that the ORR among the PD-L1 low patients is $\leq 21\%$. The alternative hypothesis is that the ORR is $> 21\%$. Assuming an ORR rate of at least 34%, with at least 110 patients, the study will have more than 82% power to demonstrate that the lower limit of the 95% two-sided confidence interval (CI) for ORR exceeds 21%, where the CI is calculated by the exact computation method. **Safety:** Safety assessments will include AEs, clinical laboratory tests, vital signs, and physical examinations. All safety data will be summarized for the All Treated Population using descriptive statistics. An IDMC was utilized for the planned safety review of the first 20 patients who received at least 2 cycles of NKTR-214 in combination with nivolumab. Subsequently a Sponsor Executive Committee (SEC) will provide formal safety reviews.



IV = intravenous; q3w = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors

NOTE: Data from the first 20 patients who received at least 2 cycles of NKTR-214 and nivolumab will be included in the initial safety review conducted by the Independent Data Monitoring Committee (IDMC) (see Section 4.1).

a. The study aims to enroll at least 110 patients whose tumors have low PD-L1 expression (based on PD-L1 IHC 22C3 PharmDx assay; see Section 4.2.5) and who have received at least one dose of NKTR-214/nivolumab; a maximum of 190 patients will be enrolled in the study, including 2 patients who received GemCarbo under Amendment 2.0 of this protocol; see Section 10.2).

1.2 Schedule of Events

Table 1: Schedule of Events (Excluding Pharmacokinetic, Immunogenicity, and [redacted] Sampling)

Procedure / Period:	Screening	Treatment							Post-treatment			
		Cycle 1 Only					Cycle 2 and Beyond		End of Treatment[w]	Follow-up[x]		Survival Follow-up[y]
Study Days[a]:	Day -28 to -1	Day 1	Day 3 (- 1 day)	Day 5 (-1 or -2 days)	Day 8 (± 3 days)	Days 14 to 21	Day 1 (± 3 days)	Day 3 (+ 2 days)	(± 7 days)	30 days from last dose (± 7 days)	100 days from last dose (± 7 days)	Every 3 months (± 14 days)
Informed consent	X											
Inclusion/ exclusion criteria	X											
Medical history	X											
Physical examination[b]	X	X					X		X	X	X	
Vital signs[c]	X	X	X		X		X		X	X	X	
ECOG performance status[d]	X	X					X		X	X	X	
ECG[e]	X											
ECHO/MUGA[f]	X											
Pregnancy test[g]	X	X					X		X	X	X	
Hematology[h]	X	X			X		X		X			
Coagulation[h]	X	X			X		X		X			
Serum chemistry[i]	X	X					X		X			
Additional laboratory assessments[j]	X						X[j]		X			
Local labs prior to dosing[k]		X					X					

Table 1: Schedule of Events (Excluding Pharmacokinetic, Immunogenicity, and [redacted] Sampling) (Contd)

Procedure / Period:	Screening	Treatment							Post-treatment			
		Cycle 1 Only					Cycle 2 and Beyond		End of Treatment[w]	Follow-up[x]		Survival Follow-up[y]
Study Days[a]:	Day -28 to -1	Day 1	Day 3 (- 1 day)	Day 5 (-1 or -2 days)	Day 8 (± 3 days)	Days 14 to 21	Day 1 (± 3 days)	Day 3 (+ 2 days)	(± 7 days)	30 days from last dose (± 7 days)	100 days from last dose (± 7 days)	Every 3 months (± 14 days)
Urinalysis (dipstick)[l]	X	X					X		X			
Serology[i]	X											
Tumor biopsy/ PD-L1 status[m]	X					X						
PK and immunogenicity assessments		Refer to Table 3										
[redacted]		[redacted]										
[redacted]		[redacted]					[redacted]					
Tumor assessment[o]	X	Every 9 weeks (± 7 days) for the first 12 months; and then every 12 weeks (± 7 days)								X	X	
Brain Imaging[p]	X	• Patients with a history of brain metastasis or symptoms should have surveillance MRI with and without contrast per standard of care. CT of the brain (with contrast) can be performed if MRI is contraindicated or not available. If contrast is contraindicated in the patient, CT of the brain without contrast can be performed. • Assessments every 9 weeks (± 7 days) from the date of enrollment through 12 months of treatment, then every 12 weeks (± 7 days) or sooner if clinically indicated.								• For patients without BICR confirmed progression, continue to have surveillance MRI/CT with and without contrast per standard of care every, 90 days (± 10 days) or sooner if clinically indicated.		

Table 1: Schedule of Events (Excluding Pharmacokinetic, Immunogenicity, and [redacted] Sampling) (Contd)

Procedure / Period:	Screening	Treatment							Post-treatment			
		Cycle 1 Only					Cycle 2 and Beyond		End of Treatment[w]	Follow-up[x]		Survival Follow-up[y]
Study Days[a]:	**Day -28 to -1**	**Day 1**	**Day 3 (- 1 day)**	**Day 5 (-1 or -2 days)**	**Day 8 (± 3 days)**	**Days 14 to 21**	**Day 1 (± 3 days)**	**Day 3 (+ 2 days)**	**(± 7 days)**	**30 days from last dose (± 7 days)**	**100 days from last dose (± 7 days)**	**Every 3 months (± 14 days)**
Administer IV fluids[q]		X					X					
NKTR-214 and nivolumab administration[r]		X					X					
Oral hydration follow-up[s]				X				X				
AE assessment	X	X	X		X	X[z]	X		X	X	X	
Review of concomitant medications/procedures	X	X	X		X	X[z]	X		X			
Health-related quality of life assessments[t]	X	X					X		X	X	X	X
Follow-up[u]										X	X	
Subsequent medications										X	X	
Subsequent anti-cancer therapy[v]										X	X	X
Survival follow-up (by telephone)												X

AE = adverse events; CT = computed tomography; CVA = cerebrovascular accident; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EOT = end of treatment; EQ-5D-3L = EuroQol Group's EQ-5D questionnaire; FFPE = formalin-fixed paraffin-embedded; IV = intravenous; LVEF =left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; Nivo = nivolumab; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; SAE = serious adverse event.

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

b. Physical examination will include a targeted physical examination on Day 1 of each cycle, which must occur within 5 days prior to administering study drugs; see Section 9.12. Body weight measurement must be performed on the day of dosing.

c. Some clinic visits will have more frequent vital sign measurements. Vital signs are to be monitored during Cycle 1 on Day 1 predose (within 2 hours of infusion). For Cycle 2 and beyond, vital signs should be monitored predose (within 30 minutes) and approximately 30 minutes after the administration of nivolumab. Blood pressure evaluation pre-dose on Cycle 1 Day 1 and on Cycle 1 Day 3 will include orthostatic blood pressure measurements. See Sections 6.2.1 and 9.13.

d. ECOG performance status assessments for Day 1 of each cycle must occur within 5 days prior to administering study drugs.

e. ECG must be done within 14 days of Day 1. See Section 9.14.

f. A standard echocardiogram or MUGA will be performed for all patients within 60 days prior to dosing Cycle 1 Day 1 to assess for cardiac function and LVEF. See Section 9.15.

g. See Section 9.7.1.

h. Screening hematology must be done within 14 days of Day 1. Cycle 1 Day 3 [redacted] (see Table 3). Hematology and coagulation assessments for Day 1 of each cycle must be drawn within 5 days prior to administering study drugs. See Appendix 2.

i. Screening serum chemistry must be done within 14 days of Day 1. Serum chemistry for Day 1 of each cycle must be done within 5 days prior to dosing. See Appendix 2.

j. See Appendix 2. The sampling for additional tests for Cycle 2 and beyond can be drawn within 5 days prior to administration of study drugs.

k. Hydration and renal function must be assessed within 24 hours, or as soon as locally feasible, by a local laboratory prior to study drug administration of each cycle. See Section 6.2.2.

l. See Appendix 2. Urinalysis assessment for Day 1 of each cycle must be provided within 5 days prior to administering study drugs.

m. Unstained FFPE, tumor tissue sections on slides (a minimum of 10 slides, preferably 15 to 25) or a FFPE tumor tissue block, collected within 12 months prior to enrollment and without intervening therapy, are acceptable in lieu of a fresh tumor biopsy prior to treatment. See Section 7.5. An optional on-treatment tumor tissue sample will be collected prior to Cycle 2 Day 1, on Days 14 to 21 of Cycle 1. Sample collection upon disease progression is optional but highly recommended. PD-L1 status is described in Section 7.3.

n. [redacted]

o. Tumor assessments at Screening and every 9 weeks (± 7 days) from Cycle 1 Day 1 (C1D1) for the first 12 months. Beyond 12 months, tumor assessments will decrease in frequency to every 12 weeks (± 7 days). A scan should also be done at EOT unless a scan was done within 4 weeks (Section 7.0). Patients who continue treatment beyond progression should continue to have scans every 9 weeks (± 7 days) for the first 12 months of treatment post-progression and every 12 weeks (± 7 days) in the second year of treatment post-progression (for a maximum treatment duration of 2 years from C1D1). Tumor assessments in the follow-up period are only needed if the patient discontinued treatment without radiographically diagnosed disease progression (Section 4.1.3.1). Patients who discontinue study treatment and do not have BICR-confirmed disease progression should continue to have scans every 90 days (± 10 days) during the follow-up period if clinically feasible, until disease progression is confirmed by BICR. Scans should continue to be collected even if a new antineoplastic regimen has been initiated. Confirmation of tumor response is discussed in Section 8.3. Scans will be sent to the imaging vendor.

p. At screening, an MRI scan of the brain is required for patients within 28 days prior to enrollment to determine the presence of CNS metastases at baseline. CT of the brain (with contrast) can be performed if MRI is contraindicated or not available. If contrast is contraindicated in the patient, CT of the brain without contrast can be performed. See Section 7.0 for further details.

q. See Section 6.2.2.

r. See Section 6.0 for additional details.

s. Between Days 3 and 5, 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 the results of the discussion. Following subsequent NKTR-214 administrations, the oral hydration follow-up should be conducted as clinically indicated for patients receiving NKTR-214 (see Section 6.2.2).

t. At each visit specified, prior to any other study assessments, health-related quality of life will be assessed using the EORTC QLQ-C30; general health status will be measured using the EQ-5D-3L and treatment burden will be captured by FACIT GP5. During survival follow-up, the EQ-5D-3L will be administered by telephone. See Section 7.7. Note, FACIT GP5 is not required to be performed at the Screening visit. FACIT GP5 must be performed after dosing on Cycle 1 Day 1; at all other study visits specified, FACIT GP5 should be performed prior to any other study assessments.

u. See Section 4.1.3.1.

v. Additional subsequent cancer 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 anti-cancer therapies will be collected.

w. See Section 4.1.3.

x. Patients must be followed for at least 100 days after the last dose of all study drugs. Follow-up Visit 1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose. Follow-up Visit 1 can be combined with the EOT Visit if the visits are within 7 days of each other. Follow-up Visit 2 occurs approximately 100 days (± 7 days) from the last dose of all study drugs. Both follow-up visits should be conducted at the clinic. See Section 4.1.3.1.

y. All patients will be contacted for post-study therapy(ies) and survival every 3 months (± 14 days) following the Day 100 follow-up visit. The study 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. See Section 4.1.3.2.

z. If the patient is not visiting the clinic for the optional biopsy or for an unscheduled visit on Days 14-21, review of AEs and concomitant medications/procedures may be conducted by telephone.

2.0 INTRODUCTION

2.1 Background

2.1.1 Bladder Cancer

Urothelial bladder cancer (UBC) is the most common cancer of the urinary system worldwide, with transitional cell carcinoma (TCC) of the bladder being the predominant histologic type and location. TCC accounts for greater than 90% of all UBC cases in the industrialized world, whereas non-urothelial subtypes, including squamous cell, adenocarcinoma, and small cell carcinoma are more frequent in other areas of the world (Chalasani, 2009). It is estimated that in 2020, there will be 81,400 new UBC cases and 17,980 deaths from UBC in the US (Siegel, 2020). Worldwide estimates for 2018 included 549,393 new cases and 199,922 deaths (Bray, 2018). UBC tends to be a cancer of older age with the average age at the time of diagnosis being 73 years (ACS, 2018).

The overall survival (OS) of bladder cancer varies widely based on stage and grade, but for metastatic UBC, the 5-year OS is 4.8% (Noone, 2018). Poor prognostic factors for survival in patients with metastatic UBC include Karnofsky performance status (KPS) less than 80% and visceral (defined as lung, liver or bone) metastasis. Median survival for patients who had zero, one, or two risk factors were 33, 13.4, and 9.3 months, respectively (Bajorin, 1999).

The preferred initial treatment for metastatic UBC is cisplatin-based combination regimens. However, approximately 50% of patients are not appropriate candidates for cisplatin-based therapies. A consensus working group has defined these medically frail patients, who are predisposed to increased toxicity from cisplatin, as those who meet any one of the following criteria (Galsky, 2011):

- Eastern Cooperative Oncology Group (ECOG) performance status of 2 or above
- Creatinine clearance less than 60 mL/min
- Grade ≥ 2 hearing loss
- Grade ≥ 2 neuropathy
- New York Heart Association (NYHA) Class III heart failure

Within this cisplatin-ineligible population, carboplatin-based combination chemotherapy is generally regarded as the preferred initial treatment. For patients who are unable to receive carboplatin-based doublets, single-agent treatment or best supportive care is recommended. The benefit of carboplatin-based therapy in medically “unfit” patients was demonstrated in the European Organization for the Research and Treatment of Cancer (EORTC) Trial 30986 (De Santis, 2012). This study evaluated 238 patients with previously untreated advanced or metastatic UBC who were unfit for cisplatin-based treatment because of either poor performance status or impaired renal function, or both. Patients were randomized to receive treatment with either gemcitabine/carboplatin (GemCarbo) or methotrexate, carboplatin, and vincristine (M-CAVI). The confirmed objective response rate (ORR) was 36% for GemCarbo and 21% for

M-CAVI. The median OS was 9.3 months in the GemCarbo arm and 8.1 months in the M-CAVI arm (p=0.64). Severe acute toxicity (death, Grade 4 thrombocytopenia with bleeding, Grade 3 or 4 renal toxicity, neutropenic fever or mucositis) was observed in 9.3% of patients receiving GemCarbo and 21.2% of patients receiving M-CAVI. Ultimately, it was concluded that while there was no significant difference in efficacy between the two treatment arms, the increased toxicity with M-CAVI warranted preferential use of GemCarbo.

While chemotherapy has historically been the mainstay of treatment for metastatic bladder cancer, the advent of immunotherapy, specifically checkpoint inhibitors (CPIs), has drastically changed the treatment landscape.

2.1.2 NKTR-214

Bempegaldesleukin is the International Nonproprietary Name (INN) for NKTR-214.

2.1.2.1 Mechanism of Action

Bempegaldesleukin (NKTR-214) is a prodrug of a conjugated cancer immunotherapy cytokine that exerts its biological activity by binding to the interleukin (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. Upon intravenous (IV) administration, the PEG chains slowly release to generate the active cytokine species (2-PEG-IL-2 and 1-PEG-IL-2) that have a peak plasma concentration 24 to 48 hours after infusion. The slow generation of the 2-PEG-IL-2 and 1-PEG-IL-2 significantly mitigates the rapid-onset, systemic cytokine-related toxicities associated with high dose IL-2.

The polymer conjugation of NKTR-214 promotes biased signaling through the IL-2 beta gamma receptor (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 intra-tumoral 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) without expanding 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 programmed cell death protein 1 (PD-1) on the surface of CD8+ T-cells and induction of a Type II interferon gene signature in the TME, driving cell surface expression of programmed cell death ligand 1 (PD-L1) on tumor cells (Diab, 2017).

The immunological properties of NKTR-214 with the induction of tumor-infiltrating lymphocytes and upregulation of the PD-1/PD-L1 axis makes NKTR-214 a potentially

promising combination therapy for use with checkpoint inhibitors that target and inhibit the PD-1/PD-L1 pathway. Moreover, the safety profile of NKTR-214 generally does not overlap with that of checkpoint inhibitors, further supporting the use of NKTR-214 as a potentially complimentary combination partner with checkpoint inhibitors.

2.1.2.2 Preclinical Effects

Nonclinical studies have shown that NKTR-214 as a single agent is efficacious in multiple murine tumor models, showing superior anti-tumor efficacy compared to aldesleukin, even when given less frequently and at lower doses (Charych, 2016a; Charych, 2017). Moreover, NKTR-214 shows apparent synergistic effects in combination with CPIs (Charych, 2016a; Charych, 2016b; Charych, 2016c) as well as adoptive cell transfer (Parisi, 2017) and provides a significant survival benefit compared to IL-2 when combined with a therapeutic peptide vaccine (Sharma, 2016). After IV administration, tumor concentrations of NKTR-214 are sustained and mirror those observed in plasma, while distribution to other tissues is low.

Nonclinical toxicology studies with NKTR-214 indicate biological activity in rats and monkeys when given at doses up to the no observed adverse effects level (0.1 mg/kg in rats and 0.03 mg/kg in monkeys) once every 14 days (q14d) for a duration of up to 3 months. All toxicities observed with NKTR-214 to date have also been reported for IL-2 (Anderson, 1989; Anderson, 1993; Harada, 1993; Ihara, 1989). Unlike aldesleukin, there was no indication of hypotension, vascular leak, or pulmonary edema, and no cardiovascular changes (blood pressure or electrocardiogram [ECG]) after administration of NKTR-214 except for an increase in heart rate in the monkey that was small in magnitude and transient. There were no toxicities associated with PEG at 10 mg/kg (q14d × 3).

2.1.2.3 Clinical Experience with NKTR-214 Monotherapy

NKTR-214 has been investigated as monotherapy in a completed Phase 1 study sponsored by Nektar:

Study 15-214-01 (EXCEL), a Phase 1 open-label, multicenter, dose escalation study of NKTR-214 in patients with locally advanced or metastatic solid tumors (n=28).

The objectives of the study were to evaluate the safety and tolerability of NKTR-214 to determine the maximum tolerated dose (MTD) as well as to assess the ORR at or below the MTD, or to identify the recommended Phase 2 dose (RP2D). NKTR-214 was administered as a 15-minute IV infusion at dose levels of 0.003, 0.006, 0.009, and 0.012 mg/kg every 3 weeks (q3w) and 0.006 mg/kg every 2 weeks (q2w).

A total of 28 patients with a mean age of 57.9 years were enrolled. All patients had received prior anti-cancer treatment and 16 (57.1%) had received immunotherapy. The majority of patients had a diagnosis of metastatic renal cell carcinoma (RCC) (15; 53.6%) or melanoma

(7; 25.0%). Patients received a median of 3 infusions of NKTR-214 (range: 1 to 25), with a median duration of exposure of 64.5 days (range: 8 to 533 days).

A summary of the clinical pharmacology, efficacy, and safety of NKTR-214 is provided below; additional information (including updated clinical data) is available in the Investigator's Brochure.

2.1.2.3.1 Clinical Pharmacology of NKTR-214

Blood samples were analyzed for NKTR-214 related cytokines (NKTR-214-RC), NKTR-214 active cytokines (NKTR-214-AC), unconjugated IL-2, and PEG to characterize the pharmacokinetics (PK) and metabolism of NKTR-214.

Maximal concentrations of NKTR-214-RC were achieved shortly after the end of the first infusion of NKTR-214 and declined monoexponentially thereafter, remaining detectable for 8 to 11 days postdose and resulting in mean half-life values of approximately 10 hours across dose levels. NKTR-214-RC maximum plasma concentrations (C_{max}) and area under the curve (AUC) increased linearly with dose.

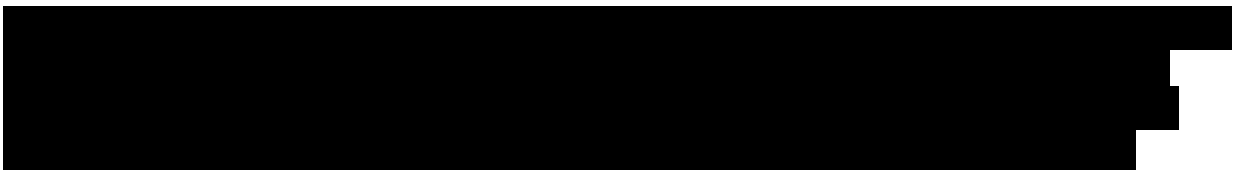
NKTR-214-AC concentrations increased gradually after dosing, achieving a mean time to C_{max} (T_{max}) between Day 2 (24 hours) and 3 (48 hours) postdose. After reaching C_{max}, NKTR-214-AC declined monoexponentially in parallel to the decline in NKTR-214-RC, and remained detectable for 8 days postdose.

NKTR-214-RC and NKTR-214-AC exposure were similar across patients within a dose cohort and between cycles, without indication of accumulation with either the q3w or q2w administration schedules, as expected based on the half-life. NKTR-214-AC and NKTR-214-RC exposure increased linearly with dose over the dose range studied.

Unconjugated IL-2 was only sporadically detected, and when detected, was present only at low concentrations (0.5 to 7.1 ng/mL, with the majority near the quantitation limit of 0.5 ng/mL), indicating that unconjugated IL-2 does not contribute to plasma NKTR-214 exposure.

After the first dose of NKTR-214, maximal total PEG concentrations were achieved shortly after the end of the infusion and declined biexponentially thereafter. Total PEG concentrations remained detectable for 15 days (336 hours) to 21 days (504 hours) postdose, i.e., prior to the next dosing cycle.

Total-PEG concentrations increased in proportion to dose. Total PEG concentrations remained detectable for 21 days, without leading to accumulation with repeat dosing.



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Lymphocytes exhibited a profile characterized by lymphopenia (Day 3) followed by gradual recovery and rebound lymphocytosis (which peaked on Days 8 to 11) following NKTR-214 administration. This is consistent with similar observations after high-dose IL-2 administration (Cesana, 2006; Gottlieb, 1989). These changes in lymphocyte concentrations were observed at all dose levels and with each treatment cycle, indicative of continuous immune system activation with each treatment cycle. In the EXCEL study, lymphocyte changes were observed, in one case, over 17 months of treatment. In the ongoing Study 16-214-02 (PIVOT-02), lymphocyte changes were observed, in several cases, over 16 months of treatment. The magnitude of the effect of NKTR-214 on lymphocytes, as characterized by the Day 8 to Day 3 ratios, increased with dose.

2.1.2.3.2 Clinical Efficacy and Safety of NKTR-214 Monotherapy

All 28 patients in Study 15-214-01 (EXCEL) were evaluable for safety and 26 were included in the Response Evaluable Population (i.e., all patients who met all eligibility criteria, had measurable disease [per Response Evaluation Criteria in Solid Tumors version 1.1, RECIST 1.1] at baseline, and also had at least one post-baseline assessment of tumor response).

All 28 patients had treatment-emergent adverse events (TEAEs), with 26 (92.9%) having adverse events (AEs) that were considered to be related to treatment. The most common treatment-related AEs were fatigue (20 [71.4%]), pruritus (18 [64.3%]), and hypotension (16 [57.1%]). The MTD of NKTR-214, based on pre-defined dose limiting toxicity (DLT) criteria, was 0.009 mg/kg administered q3w. At a higher dose (0.012 mg/kg), 1 patient experienced DLTs of Grade 3 hypotension and Grade 3 syncope, which were rapidly reversed with IV fluids; this patient continued on study and received two additional doses of NKTR-214 at 0.006 mg/kg q3w and tolerated treatment well. One patient who had a prior history of an infusion-related reaction to an immuno-oncology agent discontinued the study due to a serious adverse event (SAE) of Grade 3 infusion-related reaction (diaphoresis, rash, shortness of breath, chest tightness, tingling in tongue, low blood pressure [47/44 mm Hg], and hyperglycemia) after the first dose of NKTR-214 (0.009 mg/kg). The reaction resolved with treatment (oxygen, epinephrine, and antihistamines).

Hypotension, which is a known AE associated with both IL-2 and engineered cytokines, was identified as a principal toxicity in this study and most commonly appeared 2 to 4 days following the first infusion, coinciding with the peak plasma concentration of the active cytokines formed after administration of NKTR-214. Grade 3 hypotension (in 4 of 28 [14%] patients) was rapidly reversed with fluid administration (IV, oral, or both) and guidelines to prevent hypotension were subsequently developed (see Section 6.2.2).

Other treatment-related AEs included flu-like symptoms (chills [12 patients, 42.9%], pyrexia [10, 35.7%], and influenza-like illness [7, 25%]) as well as rash (maculo-papular [6, 21.4%], macular [5, 17.9%], erythematous [4, 14.3%], papular [3, 10.7%]) and pruritus (18, 64.3%), all

of which were predictable, manageable, and short-lived. These low-grade cytokine-related AEs generally occurred 1 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 nonsteroidal anti-inflammatory drugs (NSAIDs) and the cases of rash/pruritus were either self-limiting or treated with anti-histamines. The median duration of flu-like symptoms including fever was 3 days, and with subsequent cycles after initiating treatment with NKTR-214, these symptoms became less pronounced. It is noted that no cases of immune-mediated AEs (except one case of hypothyroidism), commonly associated with the use of checkpoint inhibitors, such as colitis, nephritis, pneumonitis, dermatitis, or hepatitis have been reported from this study.

A best overall response of stable disease occurred in 14 patients (50%) including the only patient with bladder cancer in the study; none had a complete response (CR) or partial response (PR). One patient with metastatic melanoma, who was previously treated with ipilimumab and a BRAF inhibitor and progressed, 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 and nivolumab, was treated with 19 cycles of NKTR-214 and had durable stable disease for 14 months. While no objective responses were observed, 9 patients experienced tumor shrinkage between 1% and 30%, and 2 patients, after progressing on multiple prior therapies, had durable stable disease > 1 year. Interestingly, 3 immunotherapy naïve patients receiving sequential anti-PD-1 therapy within 4 weeks of ending treatment with NKTR-214, experienced significant tumor regression at first post baseline scan. Given the biological properties of NKTR-214 and nivolumab, these observations further supported the rationale for combining these two agents.

2.1.3 Nivolumab

Nivolumab (Opdivo®) is approved for the treatment of several types of cancer in multiple regions including the United States (US; December 2014), the European Union (EU; January 2015) and Japan (July 2014). Nivolumab is also being investigated in various other types of cancer as monotherapy or in combination with other therapies.

2.1.3.1 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. CD8+ 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

CD8+ T-cell receptor (TCR) (Greenwald, 2004). Collectively, these signals govern the balance between CD8+ T-cell activation and tolerance.

PD-1 is a member of the CD28 family of CD8+ T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA (Freeman, 2000). PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression has 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 CD8+ 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 (50% effective dose [EC_{50}] 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (50% inhibitory dose [IC_{50}] ± 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 (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMCs), 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).

2.1.3.2 Nivolumab in Bladder Cancer

In Checkmate-275 (NCT02387996), 270 patients with locally advanced or metastatic urothelial carcinoma (mUC) who had disease progression during or following platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen were treated with nivolumab 3mg/kg every two weeks. The ORR was 19.6% with a median duration of response (mDOR) of 10.3 months. Further evaluating the data by PD-L1 revealed a response rate of 15.1% in patients with PD-L1 expression < 1% of tumor cells and 25% in patients with PD-L1 expression in ≥ 1% of tumor cells. These results ultimately led to approval by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in a second-line mUC population. Evaluation of nivolumab treatment in a first-line metastatic setting is currently ongoing in the Checkmate 901 study (NCT03036098).

Nivolumab has also been evaluated in combination with ipilimumab in bladder cancer (NCT 02553642) (Callahan, 2017). Forty patients with advanced or metastatic urothelial carcinoma were treated with nivolumab 3 mg/kg every 2 weeks. For patients who had a confirmed progression with monotherapy nivolumab, the study offered the option to continue

treatment with combination nivolumab plus ipilimumab (1 mg/kg every 3 weeks). The combination was dosed every three weeks for four doses followed by nivolumab monotherapy. Ten patients who were refractory to nivolumab monotherapy were treated with the combination. One patient achieved a confirmed partial response. Three additional patients achieved stable disease after documented progression, suggesting that the combination may have clinical activity in urothelial carcinoma (UC) patients who fail to respond to monotherapy checkpoint inhibition. The available data also suggest that immuno-oncology doublets may provide added benefit over monotherapy treatment in bladder cancer.

2.1.4 Clinical Experience with NKTR-214 in Combination with Nivolumab

Study 16-214-02 (PIVOT-02; NCT02983045) is an ongoing Phase 1/2 open-label, multicenter, dose escalation combination study of NKTR-214 and nivolumab in patients with select locally advanced or metastatic solid tumor malignancies. Part 1 of the study was a dose escalation phase to evaluate the safety and tolerability, and to define the MTD or RP2D of NKTR-214 in combination with nivolumab. Following determination of the RP2D (0.006 mg/kg NKTR-214 q3w plus 360 mg nivolumab q3w), Part 2 of the study is evaluating the safety and tolerability as well as the efficacy of the combination by assessing the ORR at the RP2D. The indications studied in Part 2 are melanoma, RCC, non-small cell lung cancer (NSCLC), bladder cancer, breast cancer, gastric cancer, colorectal cancer, and small cell lung cancer. Parts 3 and 4 are schedule-finding and dose expansion for the triplet, studying the safety and tolerability of NKTR-214 in combination with nivolumab (360 mg flat dose q3w) and ipilimumab (1 mg/kg) in patients with metastatic RCC, UC, melanoma, or NSCLC who are treatment-naïve.

2.1.4.1 Clinical Pharmacology

The effect of nivolumab on NKTR-214 PK was assessed based on NKTR-214-RC exposure. Pharmacokinetics of NKTR-214-RC in combination with nivolumab appear similar to those after NKTR-214 monotherapy, suggesting no drug-drug interaction between NKTR-214 and nivolumab. See Section 2.1.2.3.1 for additional NKTR-214 clinical pharmacology information.

2.1.4.2 Clinical Efficacy and Safety of NKTR-214 in Combination with Nivolumab

As of 29 October 2018, a total of 358 patients had been treated with NKTR-214 in combination with nivolumab in the ongoing Study 16-214-02 (PIVOT-02). A total of 322 (89.9%) patients had treatment-related AEs, the majority of which were mild to moderate in severity; 78 of 358 patients (34.6%) had Grade 3 treatment-related AEs. The most common treatment-related AEs (experienced by ≥ 20% of patients) were flu-like symptoms (in 62.3% of patients), rash (49.7%), fatigue (48.6%), pruritus (34.6%), nausea (28.5%), decreased appetite (26.5%) and arthralgia (20.9%). Grade ≥ 3 AEs that were considered related to NKTR-214 or nivolumab, or both, occurred in 78 patients (21.8%). These included hypotension (11 patients, 3.1%), rash (7 patients, 2.0%) diarrhea (5 patients, 1.4%), flu-like symptoms, dehydration, myalgia and vomiting (each: 4 patients, 1.1%), arthralgia, fatigue and nausea (each 3 patients, 0.8%),

asthenia and dyspnea (each 2 patients, 0.6%) and decreased appetite and pruritus (each 1 patient, (0.3%).

One hundred forty-nine patients had serious adverse events (41.6%). Of these, 58 patients (16.2%) had serious AEs that were considered related. Related treatment-emergent SAEs that were experienced by two or more patients included: flu-like symptoms (10 of 358 patients (2.8%), hypotension (7 of 358 patients, 2.0%), atrial fibrillation and dehydration (4 of 358 patients, 1.1% each), hyponatremia, pneumonitis and rash (3 of 358 patients, 0.8% each) and cerebrovascular accident, dyspnea, myocarditis, nausea and vomiting (2 of 358 patients, 0.6% each).

The NKTR-214 + nivolumab dose escalation portion of Study 16-214-02 (PIVOT-02) has been completed (n = 38), with the safety results of NKTR-214 at 0.006 mg/kg in combination with nivolumab 360 mg every 3 weeks indicating no DLTs and no Grade ≥ 3 treatment-related AEs. NKTR-214 0.006 mg/kg in combination with nivolumab 360 mg every 3 weeks was the recommended dose regimen to be taken forward into expansion cohorts in Part 2.

Tumor response data are available for the dose escalation patients as well as several of the dose expansion cohorts (melanoma, RCC, and mUC). As of 29 October 2018, 38 patients had been enrolled into the dose escalation cohorts of Study 16-214-02 (PIVOT-02) and 37 patients (11 patients with metastatic melanoma, 21 with RCC, and 5 with NSCLC) were efficacy evaluable. The remaining one patient was not considered evaluable for efficacy due to discontinuation of study due to progressive disease (PD) prior to an on-treatment CT scan. Of these 37 patients, 21 (56.8%) achieved a response by RECIST 1.1.

For the first-line melanoma and first-line RCC additional efficacy data are available. As of 29 May 2018, 26 first line (1L) RCC efficacy patients were efficacy evaluable (n = 48 enrolled; n = 26 efficacy evaluable defined as having had at least one post-baseline on treatment scan). A 46% (12 of 26 patients) ORR was noted. Responses were seen in both PD-L1 (+) (29%, 2 of 7 patients) and PD-L1 (–) (53%, 9 of 17 patients) (Diab, 2018a).

As of 11 October 2018, 38 of 41 IL melanoma patients who met the pre-specified efficacy parameters were considered efficacy evaluable. Three patients were considered not efficacy evaluable (all three patients discontinued prior to first scan due to an unrelated TEAE [n = 1] and patient decision [n = 2]). A 53% (20 of 38 patients) ORR was seen via independent central radiology review with a 24% (9 of 38 patients) CR rate. Responses were seen in both the PD-L1 (+) (defined as PD-L1 expression ≥ 1% on tumor cells) and PD-L1 (–) (defined as < 1% PD-L1 expression on tumor cells) populations with an ORR of 68% in the PD-L1 (+) population (13 of 19 patients) and 43% in the PD-L1 (–) population (6 of 14 patients) (Diab, 2018b).

2.1.4.2.1 Observed Events of Cerebrovascular Accident

2.1.4.2.1.1 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 anti-cancer 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 doublet therapy and 1 related to nivolumab only); and one of 10 (10.0%) patients who received combined NKTR-214, nivolumab, and other anti-cancer therapy (platinum-based chemotherapy) had a CVA event, which was considered by the Investigator to be unrelated to study treatment.

2.1.4.2.1.2 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 17262-01.

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 have been put in place to reduce the risk of CVA. These mitigations include implementation of a CVA adverse event management algorithm (Appendix 4) and updates to the exclusion criteria, renal function and hydration assessment, hydration guidelines, concomitant and prohibited medications, dose modification guidelines, and discontinuation criteria. Additional information on the clinical safety and risk of CVA is found in the NKTR-214 Investigator's Brochure.

2.1.4.2.2 Mitigation Measures

Following the comprehensive review of the entire NKTR-214 clinical program, additional safety measures and analyses were implemented to mitigate the risk of CVA events and to expedite reporting of CVA events by identifying CVA as an AESI. These safety measures and analyses are reflected in changes to the following protocol sections: study exclusion criteria (Section 5.2), hydration guidelines (Sections 1.2 and 6.2.2), CVA AE management algorithm (Appendix 4), [redacted] criteria to delay, resume, or permanently discontinue study drug (Section 6.5), thromboembolism prophylaxis and treatment (Section 6.7.2.1), prohibited medications (Section 6.7.4), and reporting AESI (Section 9.6).

2.1.4.3 Clinical Efficacy of NKTR-214 in Combination with Nivolumab in Urothelial Carcinoma

As of 3 December 2018, 41 patients with cisplatin-ineligible urothelial carcinoma or who refused standard of care treatment were enrolled in Study 16-214-02 (PIVOT-02; NCT02983045). The median age of these 41 patients was 70 years (range: 41 to 91); 29 were male (71%) and 12 were female (29%); 13 had PD-L1 expression ≥ 1% on tumor cells (32%) and 13 had PD-L1 expression of < 1% on tumor cells (32%), with 15 patients (37%) having unknown PD-L1 expression. The majority (22 of 41 patients [54%]) had an ECOG performance status of 1 at baseline.

The best overall response was assessed by RECIST 1.1. Of the 41 enrolled patients with cisplatin-ineligible urothelial carcinoma or who refused standard of care treatment, 27 patients had undergone at least one post-baseline (follow-up) scan and were considered efficacy evaluable. Of the other 14 patients, 1 patient was excluded from the efficacy analysis due to non-eligibility (no measurable disease), 10 were pending their first scan, and 3 discontinued study treatment prior to their first scan (1 patient decision, 1 had clinical progression; and 1 had death from disease). Among the 27 efficacy evaluable patients, the ORR (defined as a best overall response of CR or PR) was 13/27 (48%). Notably, this benefit appeared agnostic of PD-L1 status with 50% (6/12) of PD-L1(+) patients responding and 45% (5/11) of PD-L1(–) patients responding. As of the data cut-off, the median duration of follow-up was 5.1 months.

2.1.5 Recent Developments in Immunotherapy in Bladder Cancer

The development of CPIs has drastically changed the treatment landscape of mUC. Both pembrolizumab and atezolizumab have been evaluated as CPIs in the first-line treatment setting, and both received accelerated approval based on ORR and mDOR for monotherapy treatment in cisplatin-ineligible populations. While these accelerated approvals were initially agnostic to PD-L1 expression, recent health authority announcements have restricted labelling in both the EU and the US to high PD-L1 expression subpopulations (EMA, 2018; FDA, 2018).

Prior to the announcements restricting usage in low PD-L1 expression patients, monotherapy atezolizumab treatment was evaluated in cisplatin-ineligible locally advanced/mUC patients in Cohort 1 of the Phase 2, non-randomized IMvigor 210 study (NCT02951767). A total of 119 patients received treatment and an ORR of 23.5% was observed (TECENTRIQ® Prescribing Information, 2018). The mDOR in patients who responded has yet to be reached; however, the range is currently reported to be 3.7 to 16.6+ months. The median OS is 16.3 months (Balar, 2018). Further dividing this group based on PD-L1 expression by the Ventana PD-L1 (SP142) assay (PD-L1+ defined as ≥ 5% PD-L1 expression on tumor infiltrating immune cells and PD-L1– defined as < 5% expression) revealed an ORR of 28.1% in the PD-L1+ subgroup and an ORR of 21.8% in the PD-L1– subgroup. A confirmatory Phase 3 study (IMvigor 130, NCT02807636) compared the following treatments in first-line metastatic urothelial carcinoma (Galsky, 2020):

- atezolizumab with platinum-based chemotherapy (Group A)
- atezolizumab monotherapy (Group B)
- placebo plus platinum-based chemotherapy (Group C)

Addition of atezolizumab to platinum-based chemotherapy prolonged progression-free survival (PFS): median PFS was 8.2 months (95% CI 6.5–8.3) in Group A and 6.3 months (6.2–7.0) in Group C (stratified hazard ratio [HR] 0.82, 95% CI 0.70–0.96; one-sided p=0.007). Median overall survival (OS) was also prolonged with the addition of atezolizumab: 16.0 months (13.9–18.9) in Group A and 13.4 months (12.0–15.2) in Group C (0.83, 0.69–1.00; one-sided p=0.027). Median overall survival showed a nonsignificant trend toward superiority of atezolizumab alone over chemotherapy: 15.7 months (13.1–17.8) for Group B and 13.1 months (11.7–15.1) for Group C (1.02, 0.83–1.24). There were 212 (47%) confirmed objective responses (complete response [CR] + partial response [PR]) in Group A (95% CI 43–52), compared to 82 (23%) (95% CI 19–28) in Group B and 174 (44%) (95% CI 39–49) in Group C. The mDOR was 8.5 months (95% CI 7.2–10.4) in Group A, not estimable (NE) (95% CI 15.9–NE) in Group B, and 7.6 months (95% CI 6.3–8.5) in Group C. An unplanned analysis of the early survival data led to discontinuation of further accrual of patients with low PD-L1 expression to atezolizumab monotherapy (Group B).

Pembrolizumab monotherapy was also evaluated prior to the recent health authority announcements in the open label, non-randomized Phase 2 Keynote-052 study (NCT02335424). Keynote-052 enrolled 370 cisplatin-ineligible patients with locally advanced/mUC. Long-term follow-up data for Keynote-052 are available for a minimum of 2 years since the last patient enrolled (Vuky, 2020). Forty patients with CR or PR completed 2 years of study treatment, and 32 had ongoing response at completion. The overall response rate was 28.6% (95% CI, 24.1% to 33.5%). The mDOR was 30.1 months (95% CI, 18.1 months to not reached [NR]). Median OS was 11.3 months (95% CI, 9.7 to 13.1 months). Among patients with PD-L1 combined positive score (CPS) ≥ 10 (n = 110), ORR was 47.3%; 22 patients (20.0%) had CRs, and 30 patients (27.3%) had PRs. Among those with PD-L1 CPS < 10 (n = 251), ORR was 20.3%. Median DOR for the CPS ≥ 10 and CPS < 10 subgroups was NR (95% CI, 18.1 months to NR) and

18.2 months (95% CI, 9.7 months to NR), respectively; 57.0% and 45.0% had responses ≥ 24 months. In the CPS ≥ 10 and CPS < 10 subgroups, median OS was 18.5 months (95% CI, 12.2 to 28.5 months) and 9.7 months (95% CI, 7.6 to 11.5 months), respectively; 24-month OS rates were 47.0% and 24.0%, respectively.

A confirmatory Phase 3 study supporting the previously granted accelerated approval is currently ongoing (Keynote-361; NCT02853305). Similar to atezolizumab, however, enrollment of PD-L1 low patients has been halted in the monotherapy pembrolizumab arm and is currently only ongoing in combination with platinum-based chemotherapy.

EMA and FDA statements released in June 2018 (EMA, 2018; FDA, 2018) indicate that preliminary data show reduced survival for both pembrolizumab and atezolizumab when used as monotherapy for the first-line treatment of cisplatin-ineligible mUC patients with "low expression of PD-L1" as compared to chemotherapy. On recommendation from both Agencies, the labeled indications for pembrolizumab and atezolizumab for this population were subsequently modified to indicate that monotherapy treatment should only be considered in cisplatin-ineligible patients whose tumors express PD-L1 with a CPS ≥ 10 (pembrolizumab) or whose tumors have a PD-L1 expression ≥ 5% (atezolizumab) (EMA, 2018; FDA, 2018; KEYTRUDA® Prescribing Information, 2018; TECENTRIQ® Prescribing Information, 2018). Subsequently the labels were modified in the US to also allow monotherapy treatment in patients who are not eligible for any platinum-based therapy (cisplatin or carboplatin), and in the EU to also allow monotherapy treatment in patients who have had prior platinum-containing chemotherapy (KEYTRUDA® prescribing information, 2021; TECENTRIQ® prescribing information 2021; KEYTRUDA® Summary of Product Characteristics; TECENTRIQ® Summary of Product Characteristics).

The above announcements leave a significant gap in the treatment of low PD-L1 expression, first-line, cisplatin ineligible mUC patients and suggests that additional therapies may be required to enhance the efficacy of CPIs. While chemotherapy does result in significant response rates, the duration of response (DOR) is limited and the OS remains under a year. In addition, the available chemotherapy options come with significant toxicity in an older, medically frail population. These factors highlight the need for further combination immunotherapy development with the aim of improving not only efficacy but also quality of life.

2.2 Study Rationale

The mainstays of bladder cancer treatment have historically been chemotherapy and surgery. However, the emerging clinical data for single agent CPI treatment has changed the treatment landscape. While the treatment with monotherapy CPIs provides clinically meaningful durable responses in second-line (2L) and PD-L1 high 1L patients, only 20% to 45% of patients respond, suggesting that combination treatment is needed to further enhance the benefit of immunotherapy. Furthermore, patients with low PD-L1 expression have significant unmet need due to the restriction of PD-L1/PD-1 inhibitors in this population as 1L therapy.

Accumulating evidence suggests that patients with low baseline CD8+ T-cells within the tumor microenvironment (TILs) predict poor response to CPI immunotherapies (Daud, 2016a; Daud, 2016b); thus, agents designed to specifically activate and expand CD8+ T-cells may improve clinical outcomes in patients with low TILs.

NKTR-214 targets the IL-2 pathway and is designed to provide biased sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rβγ) to preferentially activate and expand NK and effector CD8+ T-cells over Treg cells. Preliminary analyses of patients' blood and tumor by flow cytometry and IHC demonstrate that NKTR-214, as a single agent, increases activated CD4+ and CD8+ T-cells in peripheral blood, with an increase in T-cell infiltrates within the tumor tissue after one dose of NKTR-214.

In addition, NKTR-214 increases PD-1 expression on T-cells in the blood and tumor after treatment with NKTR-214. In the ongoing Study 16-214-02 (PIVOT-02), at the 3 December 2018 data cut-off, 13 matched tumor tissue samples from baseline and Cycle 1 Days 15 to 21 in UC patients were available for evaluation. Of these matched samples, 10 had PD-L1 expression of < 1% on tumor cells at baseline and 3 had PD-L1 expression of ≥ 1% on tumor cells. Seven of the 10 (70%) PD-L1 low baseline samples converted to high by week three of treatment. The ability to alter the immune environment and increase PD-1 expression on effector CD8+ T-cells and tumor may improve the effectiveness of anti-PD-1 blockade.

The current study aims to demonstrate that treatment with NKTR-214 in combination with nivolumab will be efficacious in patients with locally advanced or mUC who are ineligible for cisplatin treatment. The available efficacy data from the ongoing Study 16-214-02 (PIVOT-02), as well as the correlative data suggesting that NKTR-214 has the ability to alter the immune environment and increase PD-L1 expression, provides strong rationale for further exploration of the combination in 1L cisplatin ineligible locally advanced or mUC in patients with tumors that have low PD-L1 expression. In addition, the available data in patients whose tumors have high PD-L1 expression suggest additional benefit can also be conferred in this population.

PD-L1 expression will be assessed using the PD-L1 IHC 22C3 pharmDx assay, which is approved for use with pembrolizumab in UC (P150013/S0011; Dako North America, Inc. 2018). The cut-off point defining low PD-L1 expression will be CPS < 10 (see Section 7.3). In this protocol, patients with tumors that have low PD-L1 expression will be referred to as low PD-L1 patients. Patients with CPS ≥ 10 will be considered to have high PD-L1 expression and will be referred to as high PD-L1 patients (see Section 7.3).

2.3 Benefit/Risk Aspects

2.3.1 NKTR-214 Safety Profile

NKTR-214 was designed to mitigate the serious 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, serum creatinine elevations), infusion-related reactions/hypersensitivity reactions, thyroid dysfunction, arthralgia, and eosinophilia. 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 with NKTR-214 at the doses tested.

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

2.3.2 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, most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies).

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

2.3.3 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 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 patients to PD-L1 positive patients suggests that the addition of NKTR-214 to a checkpoint inhibitor (nivolumab) may change the tumor microenvironment in PD-L1 negative patients such that the combination may contribute to anti-tumor activity 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 with limited alternative treatment options warrants continued evaluation of the combination of NKTR-214 and nivolumab in the clinical setting and supports further development of the combination in patients with cancer.

2.3.4 Independent Data Monitoring Committee

In addition to routine safety monitoring and pharmacovigilance activities, an Independent Data Monitoring Committee (IDMC) provided an initial safety review; subsequently a Sponsor Executive Committee (SEC) will provide formal safety reviews. The IDMC/SEC are described further in Section 10.11.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is:

- To evaluate the anti-tumor activity of NKTR-214 in combination with nivolumab by assessing the ORR by RECIST 1.1 per blinded independent central review (BICR) in patients whose tumors have low PD-L1 expression

3.2 Secondary Objectives

The secondary objectives are:

- To evaluate the effect of NKTR-214 in combination with nivolumab by assessing the ORR by RECIST 1.1 per BICR in all treated patients
- To evaluate the effect of NKTR-214 in combination with nivolumab by assessing DOR by RECIST 1.1 per BICR in all treated patients and patients whose tumors have low PD-L1 expression
- To evaluate the effect of NKTR-214 in combination with nivolumab by assessing the ORR and DOR by RECIST 1.1 per Investigator assessment in all treated patients and patients whose tumors have low PD-L1 expression
- To evaluate the safety and tolerability of NKTR-214 in combination with nivolumab

4.0 INVESTIGATIONAL PLAN

4.1 Study Design

This is a single-arm, Phase 2 study evaluating the safety and efficacy of NKTR-214 in combination with nivolumab in cisplatin ineligible patients with locally advanced or metastatic UC. Patients will be able to enroll regardless of their baseline PD-L1 expression. The study aims to enroll at least 110 patients whose tumors have low PD-L1 expression and who have received at least 1 dose of NKTR-214/nivolumab.

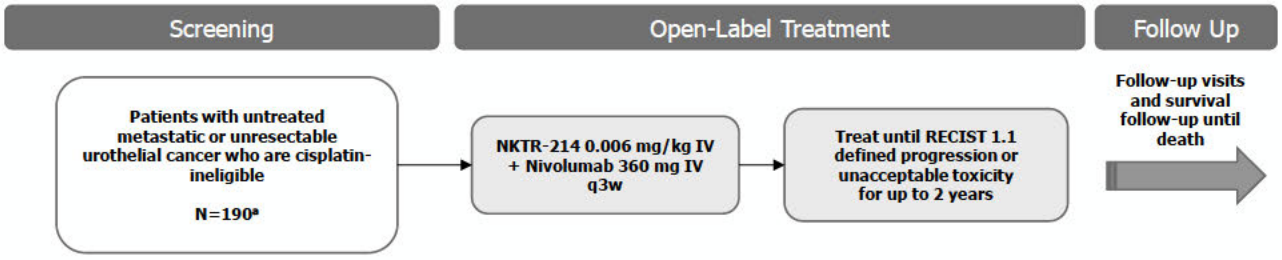
The study has a Screening period, Treatment period, Follow-up period, and Survival Follow-up Period. Patients will receive the following treatment:

- NKTR-214 0.006 mg/kg IV and nivolumab 360 mg IV q3w (on Day 1 of each 3-week cycle).

This study was initially monitored by an IDMC (see Section 10.11). The IDMC conducted the initial review on safety and other relevant data from the first 20 patients who received at least 2 cycles of study treatment (6 weeks). Additional patients continued to be enrolled while the IDMC conducted this review. Following this review, subsequent safety reviews are being conducted by the Sponsor Executive Committee (SEC). Details are provided in the IDMC charter.

Figure 2 provides the study schematic and Table 1 outlines the study procedures in the Schedule of Events.

Figure 2: Study Schematic



IV = intravenous; q3w = every 3 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1

NOTE: Data from the first 20 patients who received at least 2 cycles of NKTR-214 and nivolumab will be included in the initial safety review conducted by the Independent Data Monitoring Committee (IDMC) (see Section 4.1).

a. The study aims to enroll at least 110 patients whose tumors have low PD-L1 expression (based on PD-L1 IHC 22C3 PharmDx assay; see Section 4.2.5) and who have received at least one dose of NKTR-214/nivolumab; a maximum of 190 patients will be enrolled in the study, including 2 patients who received GemCarbo under Amendment 2.0 of this protocol see Section 10.2).

4.1.1 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 informed consent form (ICF), patients will be evaluated for entry criteria during the Screening period within 28 days before administration of study drugs. Blood for hematology and chemistry laboratory evaluations must be drawn within 14 days prior to the first study treatment; ECG must also be done within 14 days prior to the first study treatment. 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 24 hours prior to the start of study (see Appendix 3). Rescreening after screen failure will be allowed once. A new ICF will be signed if a patient is rescreened.

Patients must either consent to and undergo a screening biopsy at study entry to document PD-L1 status (see Section 7.3) or provide archival formalin-fixed paraffin-embedded (FFPE) tissue, either as a block or unstained slides (minimum of 10, preferably 15-25 slides). Archival tissue must be obtained within 12 months prior to enrollment and with no intervening treatment.

4.1.2 Treatment Period

All biopsy and archival tissue will be sent to a central laboratory for PD-L1 evaluation (see Section 7.3). A valid tracking number confirming shipment of the tissue to the central laboratory must be available prior to Cycle 1 Day 1.

The treatment period of the study will consist of multiple 21-day (3-week) cycles with associated evaluations and procedures. Each cycle is defined by the frequency of NKTR-214 and nivolumab administration (q3w).

Every effort should be made to schedule visits within the protocol-specified windows (Table 1).

Patients will be treated until disease progression by RECIST 1.1 or loss of clinical benefit, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the patient decision to discontinue treatment or withdraw consent, the patient is lost to follow-up, Sponsor decides to terminate the study, or for a maximum of 2 years of treatment on NKTR-214/nivolumab (see Section 4.1.3 for additional details).

Accumulating evidence indicates that a minority of patients with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Given this, patients with PD per RECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator.

For the patients who continue NKTR-214/nivolumab study treatment beyond progression, the study treatment should be discontinued permanently if an additional 10% or more increase is seen in the total tumor burden, with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and the diameters of new

measurable lesions compared to the time of initial PD. A new lesion is measurable if the longest diameter is at least 10 mm except for pathological lymph nodes, which must have a short axis of at least 15 mm. Any new lesions that are non-measurable at the time of initial appearance and become measurable later will be included in the calculation of total tumor burden. In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

Patients will be permitted to continue on treatment beyond initial RECIST 1.1-defined PD as long as they meet the following criteria:

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

The assessment of clinical benefit should take into account whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment. The patient must sign the treatment beyond progressive disease ICF prior to continuing study treatment. Patients who continue NKTR-214/nivolumab study treatment beyond progression will be allowed to be treated with NKTR-214/nivolumab for a maximum of 2 years from first dose of study treatment (C1D1).

4.1.3 End of Treatment

Patients may choose to discontinue the study 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. The end of treatment (EOT) visit should occur ± 7 days after study therapy is permanently discontinued or before a new antineoplastic regimen starts. Radiographic tumor assessment is needed at EOT unless done within 4 weeks prior to the EOT visit.

Reasons for EOT are listed below:

- Disease progression in the absence of clinical benefit as determined by the Investigator.
- Occurrence of a clinically significant AE found to be unacceptable or non-resolution of a clinically significant AE for > 8 weeks.
- Symptomatic deterioration in the absence of tumor progression per RECIST 1.1.
- Noncompliance of the patient with protocol-mandated procedures based on the judgment and agreement of both the Investigator and Sponsor.

- At the discretion of the Investigator (continued participation is no longer in the patient's best interest in the opinion of the Investigator).
- Pregnancy in a female patient.
- Patient's decision to discontinue treatment.
- Lost to follow-up (defined as after 3 attempts at contact by phone followed by 1 attempt by sending a certified letter).
- The study is terminated by the Sponsor.
- Patient has been treated with NKTR-214/nivolumab for a maximum of 2 years from the first dose of study treatment (C1D1).

In the event of a patient's withdrawal, the Investigator will promptly notify the Sponsor and make every effort to complete the EOT procedures specified in the Schedule of Events (Table 1).

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

4.1.3.1 Follow-Up

After patients complete the End of Treatment visit, follow-up should continue until patient withdrawal of consent , death, loss to follow-up, or study termination by the Sponsor. Timing for follow-up will be as follows:

- Assessments should continue as described in Table 1.
- Patients must be followed for at least 100 days after the last dose of all study drugs. Follow-up Visit 1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose. Follow-up Visit 1 can be combined with the EOT Visit if the visits are within 7 days of each other. Follow-up Visit 2 occurs approximately 100 days (± 7 days) from the last dose of all study drugs. Both follow-up visits should be conducted at the clinic.
- Patients should be followed as clinically indicated.
- Radiologic tumor assessments will occur every 90 (± 10) days from the last radiologic assessment and continue to be collected even if a new antineoplastic regimen has been initiated, until disease progression, patient withdraws consent, death, or study termination by the Sponsor.
- In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drugs. If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

4.1.3.2 Survival Follow-Up

All patients will be contacted for post-study therapy(ies), quality of life assessments, and survival every 3 months (± 14 days) following the Day-100 follow-up visit (Follow-up Visit 2) or following last contact with the patient, if Follow-Up Visit 2 is missed.

- Survival visits may be conducted in person or by telephone.
- Information about subsequent cancer 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. 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. Additional subsequent cancer 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.

4.1.4 End of Study

The start of the study is defined as first visit for first patient screened. End of study is defined as the last visit or scheduled procedure shown in Table 1 for the last patient. The total duration of the study is up to 5 years from enrollment of the last patient, or until the time of OS analysis, whichever occurs earlier.

Note that the maximum duration of treatment with NKTR-214 and nivolumab for any patient is 2 years (see Section 4.2.2).

4.1.5 Treatment After End of Study

At the conclusion of the study, patients who continue to demonstrate clinical benefit may be eligible to receive Nektar-supplied study treatment for the maximum treatment duration (as specified in Section 4.1.2). Study treatment may be provided via an extension of the study, a rollover study requiring approval by the responsible health authority and ethics committee, or through another mechanism, at the discretion of Nektar.

Nektar reserves the right to terminate access to Nektar-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab and NKTR-214 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases Nektar will follow local regulations (Section 11.0).

4.1.6 Patients Enrolled onto Gemcitabine/Carboplatin (GemCarbo) Treatment in an Earlier Version of the Protocol

For patients enrolled to GemCarbo on a prior protocol amendment, please see Appendix 5.

4.2 Rationale for Study Design Elements

4.2.1 Choice of Endpoints

This study will use the primary endpoint of ORR in patients with low PD-L1 expression. ORR will be assessed per RECIST 1.1 by a BICR. ORR will further be described by the durability and depth of responses, as those aspects are important characterizations of responses with immune-oncology treatments.

4.2.2 Duration of Treatment with Nivolumab / NKTR-214

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical studies 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 (Brahmer, 2015; Borghaei, 2015; Hellmann, 2017; Larkin, 2015; Motzer, 2015), and emerging data suggest 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). Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment (Schadendorf, 2015).

Accumulating data suggest that 2 years of PD-1 CPI treatment may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion study evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 patients with 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% to 18% for squamous and non-squamous NSCLC respectively) (Felip Font, 2017).

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized Phase 3 study of pembrolizumab (at either 2 mg/kg or 10 mg/kg q3w) versus docetaxel in patients with previously treated, high PD-L1, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (hazard ratio [HR] 0.72, P = 0.00017) and

pembrolizumab 10 mg/kg (HR 0.60, P < 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. Of 556 patients randomized to pembrolizumab, 104 (19%) 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% confidence interval [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 immuno-oncology treatment beyond 2 years in advanced tumors. 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 the start of study treatment.

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 to match the duration of nivolumab therapy.

4.2.3 Justification for Dose

4.2.3.1 NKTR-214

The dose for NKTR-214 is 0.006 mg/kg IV q3w for adults, taking into consideration the clinical safety profile associated with the robust immune system activation observed in Study 16-214-02 (PIVOT-02) (see Section 2.1.4). NKTR-214 dose is based on the IL-2 protein component. Please refer to Section 2.1.4 for additional details on Study 16-214-02 (PIVOT-02).

4.2.3.2 Nivolumab

Nivolumab monotherapy has been extensively studied in multiple tumor types, including urothelial carcinoma, melanoma, NSCLC, RCC, classical Hodgkin's lymphoma (cHL), and squamous cell carcinoma of the head and neck (SCCHN), 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 UC, melanoma, NSCLC, RCC, cHL, and SCCHN, using a regimen of either nivolumab 240 mg q2w, nivolumab 3 mg/kg q2w, and nivolumab 480 mg q4w.

Nivolumab has been shown to be safe and well tolerated up to a dose level of nivolumab 10 mg/kg q2w. Population PK (PPK) analyses have shown that the 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 predicted 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 C_{max} 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.

Finally, nivolumab 360 mg q3w is currently being investigated in combination with a number of other agents, including NKTR-214 in Study 16-214-02 (PIVOT-02) (see Section 2.1.4.2), 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. Further details on nivolumab 360 mg q3w dosing can be found in the Investigator's Brochure.

4.2.3.3 Rationale for NKTR-214 / Nivolumab Combination Dose

Given the totality of data for NKTR-214 monotherapy (see Section 2.1.2.3) and for NKTR-214 in combination nivolumab (see Section 2.1.4), including safety/tolerability, reproducible PK,

dose-independent pharmacodynamic profile, immune cell activation, and promising efficacy data, NKTR-214 0.006 mg/kg IV q3w plus nivolumab 360 mg IV q3w is considered as the appropriate dose to be administered in Phase 2 and 3 studies.

4.2.4 Rationale for Open-label Design

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

4.2.5 Choice of PD-L1 Assays

Patients will be able to enroll regardless of PD-L1 status. PD-L1 expression will be assessed using the PD-L1 IHC 22C3 pharmDx assay approved for use with pembrolizumab in UC (P150013/S0011; Dako North America, Inc., 2018). This assay was selected based on the FDA announcement on 16 August 2018 identifying the assay as a companion diagnostic to select patients with locally advanced or metastatic urothelial carcinoma who are cisplatin-ineligible for treatment with Keytruda (FDA, 2018).

This assay is further described in Section 7.3. In addition to utilizing the PD-L1 IHC 22C3 pharmDx assay, unstained tissue sections may be assessed retrospectively for membranous tumor and/or immune cell PD-L1 expression using other IHC antibody assays.

5.0 SELECTION OF STUDY POPULATION

5.1 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.
2) Histologically or cytologically documented urothelial cell carcinoma (also termed TCC) including renal pelvis, ureters, urinary bladder, and urethra that is inoperable, locally advanced (T4b, any N; or any T, N2-3) or metastatic (M1, Stage IV).
   - Histologically or cytologically confirmed locally advanced and unresectable or metastatic urothelial cancer, including mixed urothelial cell and non-urothelial cell histologies. If the histology is mixed with non-urothelial carcinoma (e.g., squamous cell carcinoma), the urothelial cell component must be dominant (> 50% of the total histology).
3) Tumor tissue is required to be analyzed by the central laboratory to document PD-L1 status.
   - Tissue can be provided in one of two ways:
     (1) A new biopsy taken during screening
     (2) Archival tissue from either a FFPE tissue block or unstained tumor tissue sections (see Section 7.5). Archival tissue must be obtained within 12 months prior to enrollment and with no intervening treatment.
   - A tracking number confirming shipment of the sample to the central laboratory must be supplied prior to Cycle 1 Day 1.
4) Male or female patients, age 18 years or older at the time of signing the ICF.
5) ECOG performance status ≤ 2 (see Appendix 1).
6) Measurable disease per RECIST 1.1 criteria.
7) No prior systemic chemotherapy or investigational agent for inoperable locally advanced or mUC.
   - For patients who received prior perioperative chemotherapy for urothelial bladder cancer, a treatment-free interval of > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment naïve in the metastatic setting.
   - Patients must not have received neoadjuvant or adjuvant therapy with any immuno-oncology regimens.
   - Prior local intravesical chemotherapy or immunotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment.

8) Ineligible for cisplatin as defined by any one (or more) of the following criteria:
   a) Impaired renal function (calculated by Cockroft-Gault or measured by 24-hour urine collection) defined as a creatinine clearance (CrCl) ≥ 30 but < 60 mL/min.
   b) Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 Grade ≥ 2 hearing loss
   c) CTCAE v 5.0 Grade ≥ 2 peripheral neuropathy
   d) ECOG performance status of 2
9) Prior palliative radiotherapy must be completed at least 2 weeks prior to study drug administration. Patients must have recovered from all Grade 2 or higher radiation-related toxicities. Note: radiated lesions cannot be used as measurable lesions unless there is clear evidence of progression.
10) Demonstrated adequate organ function, as defined below, within 14 days of treatment initiation
   a) White blood cell (WBC) count ≥ 2000/μL (after at least 7 days without growth factor support)
   b) Absolute neutrophil count (ANC) ≥ 1500/μL (after at least 7 days without growth factor support)
   c) Platelet count ≥ 100×10^3/μL
   d) Hemoglobin ≥ 9.0 g/dL (no transfusions within 7 days of laboratory test)
   e) CrCl rate ≥ 30 mL/min (using the Cockcroft-Gault formula) or directly measured by 24-hour urine:

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{creatinine in mg/dL}} \times 0.85$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{creatinine in mg/dL}} \times 1.00$$

   f) Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤ 3 × upper limit of normal (ULN)
   g) Total bilirubin ≤ 1.5 × ULN (except patients with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
11) A documented left ventricular ejection fraction (LVEF) > 45% using standard echocardiogram or multigated acquisition (MUGA) scan test taken within 60 days prior to Cycle 1 Day 1.
12) WOCBP must have a serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.

- Women must not be breastfeeding
- WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment and for 5 months post-treatment completion. Women should use an adequate method(s) of contraception as indicated in Appendix 3. WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.
- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 3) for the duration of treatment with study treatment(s) and 3 months after the last dose of NKTR-214. In addition, male patients must be willing to 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 3), which have a failure rate of < 1% when used consistently and correctly.

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

5.2 Exclusion Criteria

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

1) Female patients who are pregnant or lactating, who plan to get pregnant, or who have a positive serum or urine pregnancy test.
2) Active brain metastases or leptomeningeal metastases. 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 Cycle 1 Day 1). There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to Cycle 1 Day 1. Stable dose of anticonvulsants is allowed. Treatment for CNS metastases may include whole brain radiation, stereotactic radiosurgery (e.g., GammaKnife, CyberKnife, or equivalent) or neurosurgical resection. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 28 days prior to Cycle 1 Day 1 are not eligible.
3) Prior active malignancy within the previous 3 years except for locally curable cancers with negligible risk of metastases or death that have been treated with expected curative outcome, such as basal or squamous cell skin cancer, carcinoma in situ of the prostate, cervix, or breast. An incidental finding of prostate cancer (identified upon resection of the prostate) is acceptable, provided that one of the following criteria is met: T2N0M0, or Gleason score ≤ 3+4, or prostate-specific antigen (PSA) below upper limit of normal by local laboratory and not requiring active treatment.

4) Patients who have an active known or suspected autoimmune disease. Patients requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease that requires systemic steroids or immunosuppressive agents. (Exceptions include any patient on 10 mg or less of prednisone or equivalent, patients with vitiligo, hypothyroidism stable on hormone replacement, Type I diabetes, Graves' disease, Hashimoto's disease, alopecia areata, eczema, or psoriasis.)
5) Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of Cycle 1 Day 1. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
6) Patients must not have received prior IL-2 therapy.
7) Patients who have received any live/attenuated vaccine within 30 days before Cycle 1 Day 1.
8) Prior treatment with an anti PD-1, anti PD-L1, anti-PD-L2, or anti CTLA-4 antibody, agents that target IL-2 pathway, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
9) History of allergy to study drug components.
10) History of severe hypersensitivity reaction to any monoclonal antibody.
11) History of organ, hematopoetic, or tissue transplant that requires the systemic use of immunosuppressive agents.
12) Active infection requiring systemic therapy within 14 days prior to Cycle 1 Day 1.
13) Any positive test result for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating presence of virus, e.g., hepatitis B surface antigen (HBsAg) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).
14) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.
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 (NYHA Class III or IV)
    d) Uncontrolled clinically significant arrhythmias
16) History of pulmonary embolism (PE), deep vein thrombosis (DVT), or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event (e.g., internal jugular vein thrombosis) within 3 months prior to enrollment.

- Patients with a history of a venous or arterial thromboembolic event must be asymptomatic for at least 2 weeks prior to enrollment and must be receiving a stable regimen of therapeutic anticoagulation (preferably low molecular weight heparin [LMWH] or direct oral anticoagulation [DOAC]; see Section 6.7.2.1 for further guidance).
- 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 in the study (i.e., through the end-of-treatment [EOT] visit).

17) Need for > 2 antihypertensive medications for management of hypertension (including diuretics). Patients with hypertension must be on a stable antihypertensive regimen (defined as no dose adjustments to antihypertensive medications) for the 14 days prior to Cycle 1 Day 1. Note: An antihypertensive medication that contains 2 drugs with antihypertensive effects in one formulation is counted as 2 antihypertensive drugs (e.g., angiotensin-converting-enzyme [ACE] inhibitor plus diuretic; calcium channel blocker plus ACE inhibitor).

18) Patients with inadequately treated adrenal insufficiency.

19) Known current drug or alcohol abuse.

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

21) Vulnerable populations as described by local public health code, as applicable per country.

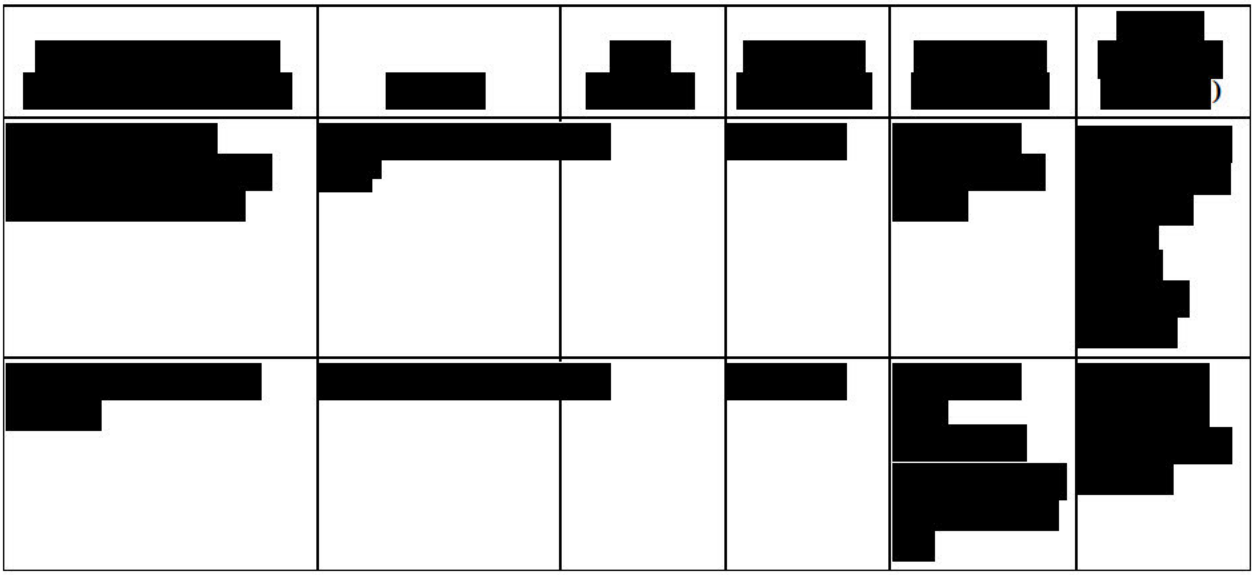
22) Legally protected majors or majors who are unable to express their consent as described by their local public health code, as applicable per country.

6.0 STUDY TREATMENTS

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- Bempegaldesleukin (NKTR-214) Powder for Solution for Injection
- Nivolumab Solution for Injection

Table 2: Study Treatments for 18-214-10



IMP = investigational medicinal product

a. [redacted]

6.1 Administration of Study Drugs

6.1.1 Bempegaldesleukin (NKTR-214)

Bempegaldesleukin is the International Nonproprietary Name (INN) for NKTR-214.

6.1.2 Drug Description and Formulation

[redacted]

[redacted]

6.1.3 Drug Packaging and Labeling

[redacted]Each vial will be labeled according to good manufacturing practices and local regulatory requirements.

6.1.4 Drug Reconstitution and Handling

NKTR-214 will be administered first, before nivolumab. NKTR-214 is to be administered as an IV infusion over 30 ± 5 minutes at a starting dose of 0.006 mg/kg every 3 weeks. Nivolumab administration should start at least 30 minutes from the end of the NKTR-214 administration. Patients may be dosed no less than 18 days from the previous dose.

[redacted]

The instructions for reconstitution, preparation, and administration of NKTR-214 Drug Product are described in the Pharmacy Manual.

6.1.5 Nivolumab

Patients should receive nivolumab at a dose of 360 mg as a 30-minute (± 5 minutes) IV infusion on Day 1 of each treatment cycle. Nivolumab should be given at least 30 minutes after the completion of the NKTR-214 infusion.

There will be no dose escalations or reductions of nivolumab allowed. Patients may be dosed no less than 18 days from the previous dose during q3w cycles. 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 directions in Section 6.6.4. Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the patient tolerates the treatment (see Section 6.5).

Nivolumab injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL), is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. For the fixed dose (e.g., 360 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab infusions are compatible with polyvinyl chloride or polyolefin containers and infusion sets, and glass bottles.

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

6.2 Monitoring, Vital Signs, and Hydration Guidelines

The study site must be equipped for medical emergencies.

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 6.6.4. If the patient experiences a Grade ≥ 2 infusion-related reaction or hypotension during the days after NKTR-214 dosing, the patient may be monitored overnight at the discretion of the Investigator; longer periods of monitoring may be implemented at the discretion of the Investigator.

Treatment with NKTR-214 may be delayed or reduced as described in Section 6.5. NKTR-214 treatment can continue in the event that nivolumab is permanently discontinued due to toxicities; see Section 6.5.5.

6.2.1 Frequent Vital Signs

Vital signs are to be monitored during Cycle 1 as follows:

- Cycle 1 Day 1 Predose including orthostatic blood pressure measurements (within 2 hours of infusion); see Section 9.13
- Cycle 1 Day 1 Postdose: within 30 minutes after infusion of nivolumab
- Cycle 1 Day 3: Including orthostatic blood pressure measurement; see Section 9.13
- Cycle 1 Day 8

For Cycle 2 and beyond, vital signs should be monitored as follows:

- Predose (within 30 minutes)
- approximately 30 minutes after the administration of nivolumab

If the patient experiences a Grade ≥ 2 infusion-related reaction or hypotension during the days after NKTR-214/nivolumab dosing, the patient may be monitored overnight at the discretion of the Investigator. Longer periods of monitoring may be implemented at the discretion of the Investigator.

6.2.2 Hydration Guidelines

Important safety information and hydration instructions are to be provided to patients. Hydration and renal function should be assessed within 24 hours prior to study drug administration or as soon as locally feasible. Underlying reasons for decreased oral intake (such as nausea) should be addressed and treatment (such as IV hydration) should be provided. Patients may receive additional hydration precautions in a patient card/handout.

For those patients assigned to NKTR-214, administer at least 1 liter of IV fluid on NKTR-214 dosing days (Day 1 of cycle). For the next 3 days (Days 2-4) after administration of NKTR-214, patients are to be instructed to drink at least 2 liters per day of self-administered oral hydration. Advise patients to refrain from activities that may contribute to dehydration (including but not limited to, strenuous activity, long hot showers, and saunas) for Days 1 to 4 of each cycle of treatment with NKTR-214. Advise patients with orthostatic symptoms to call their treating oncologist and consider increasing oral hydration.

Between Days 3 and 5, inclusive, following administration of the first 2 doses of NKTR-214, site personnel must contact the patient (by telephone or clinic visit) at least once to remind the patient of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion (Section 2.2). Following subsequent NKTR-214 administrations, the oral hydration follow-up should be conducted as clinically indicated for patients receiving NKTR-214.

Per clinical judgment, IV fluids may be administered at any time. 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 to be in the best interest of the patient (e.g., evidence of fluid overload).

6.2.3 Hypotension Guidelines

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 hyperplasia), particularly when therapy involves multiple anti-hypertensive drugs and classes other than thiazide diuretics. If withholding antihypertensive medications, withhold no less than 12 hours and no more than 48 hours prior to each dose of NKTR-214. Patients who are on medications with antihypertensive effects for the treatment of coronary artery disease (CAD) (e.g., β-blockers, Ca channel blockers, nitrates, etc.) should be able to temporarily discontinue these drugs prior to initiation of treatment.

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

In patients receiving beta-blockers, consider a step-wise tapering of doses before initiation of NKTR-214 to avoid reflex tachycardia. If Grade 2 or higher 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.

Adequate hydration mitigates the development of hypotension associated with NKTR-214 administration (see Section 6.2.2).

Per clinical judgment, IV fluids may be administered at any time. The Investigator may decide to forego administering IV fluids to a patient or adjust the recommendation for self-administered oral hydration to a particular patient if this is deemed in the best interest of the patient (e.g., evidence of fluid overload).

Patients with pre-existing adrenal impairment requiring corticosteroid supplementation may be at increased risk for hypotensive episodes during treatment with NKTR-214. For these patients, it may be necessary to provide additional corticosteroid support (see Section 6.7.2 for details).

6.3 Method of Treatment 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 enrollment and drug supply.

6.4 Blinding

Not applicable.

6.5 Dosage Modification

Dose modification for NKTR-214 and nivolumab 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.

In the event that nivolumab is permanently discontinued due to toxicities, NKTR-214 can continue to be administered. Likewise, if NKTR-214 is permanently discontinued, nivolumab can continue to be administered. Any dose reductions will require discussion and consultation with the Medical Monitor.

Note: tumor assessments for all patients should continue as per protocol even if dosing is delayed.

Patients who require delay of nivolumab or NKTR-214 should be re-evaluated weekly or more frequently if clinically indicated and resume treatment with combination of NKTR-214 and nivolumab (on Day 1 of the next cycle) when re-treatment criteria are met. 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.

6.5.1 NKTR-214 Dose Modifications and Delays

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 administration should be delayed or reduced for the following reasons:

- For persistent Grade 2 related toxicity, 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 (or as soon as locally feasible). For further guidance, refer to the Renal AE Management Algorithm in the current nivolumab Investigator's Brochure.

- Grade ≥ 3 toxicity at least possibly related to NKTR-214: NKTR-214 dosing must be delayed until resolution to Grade 1 or baseline (unless the toxicity otherwise requires permanent discontinuation per Section 6.5.5), 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 6.5.4).
- 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 NKTR-214 dose or at a lower NKTR-214 dose level when toxicity resolves to Grade 1 or returns to baseline, except for instances where the potential recurrence of the event poses an undue risk for the patient. Medical Monitor consultation is required for dose reduction.

6.5.2 Nivolumab Dose Delay 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, total bilirubin will require dose discontinuation (unless satisfying the Cycle 1 AST/ALT elevation criteria outlined in Section 6.5.3)
- 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 6.5.4).
- Any AE, 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 re-treatment criteria are met.

6.5.3 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 judgement. Subsequent cycles should follow the standard Hepatic Adverse Event Management Algorithm in the current nivolumab Investigator's Brochure.

Rule out non-inflammatory etiologies. Consider imaging if obstruction is suspected. If non-inflammatory cause, treat accordingly and continue NKTR-214 and nivolumab.

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

- **AST or ALT > 3.0 to ≤ 5 × ULN (within first cycle of NKTR-214 and nivolumab)**

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

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

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

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

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

  If no improvement within 7 days (follow the Hepatic Adverse Event Management Algorithm in the nivolumab Investigator's Brochure for appropriate management);

  - Discontinue NKTR-214 and 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 in the nivolumab Investigator's Brochure for appropriate management)**

  - Discontinue NKTR-214 and nivolumab
  - Increase frequency of monitoring to approximately 1-2 days
  - Treat with 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 6.5.5 for discontinuation criteria.

6.5.4 Criteria to Resume NKTR-214 and/or Nivolumab Dosing

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

- Patients who delayed dosing for acute infection requiring systemic antibiotic therapy must be free of signs or symptoms of infection for 72 hours after completion of antibiotic therapy prior to resuming study treatment.
- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- 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 resuming treatment. 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 Medical Monitor (or designee).
- Patients with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor (or designee). Grade ≥ 3 adrenal insufficiency or Grade ≥ 4 hypophysitis require discontinuation regardless of control with hormone replacement. 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 Section 6.5.1), delay retreatment with study drug for approximately 3 to 5 days. After the dosing delay, the patient may resume study drug when serum creatinine has returned to Grade ≤ 1, as assessed within 24 hours or as soon as locally feasible, prior to redosing with study drug, except where permanent discontinuation of study drug is required (see Section 6.5.5).

6.5.5 Permanent Treatment Discontinuation Criteria

Patients meeting any of the following criteria will be required to permanently discontinue all assigned study drug(s). However, per Investigator assessment, treatment with NKTR-214 or nivolumab alone may continue as a monotherapy if the toxicities listed below are considered related to only one of the study drugs, and once the criteria to resume are met (Section 6.5.4). For

CVA events and suspected TIA events, follow the criteria described below (additional details are provided in the CVA management algorithm in Appendix 4).

- 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 8 weeks or requires systemic treatment.
- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve following dose delay and systemic steroids (also see Pulmonary Adverse Event Management Algorithm in the nivolumab Investigator's Brochure).
- Any ≥ Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, endocrinopathies, and laboratory abnormalities:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, or hypersensitivity reaction of any duration requires discontinuation.
    - Grade 3 drug-related endocrinopathies (excluding adrenal insufficiency) adequately controlled with only physiologic hormone replacement do not require discontinuation.
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with clinically significant bleeding requires discontinuation.
        - Any drug-related liver function test abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm in the nivolumab Investigator's Brochure):
            - AST or ALT > 5 × ULN to 8 × ULN for > 2 weeks
            - AST or ALT > 8 × ULN
            - Total bilirubin > 5 × ULN
            - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN

In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. 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/designee must occur. For IL-2-mediated ALT/AST elevations < 8.0 × ULN in Cycle 1 only, study treatment does not need to be discontinued (see Section 6.5.3).

- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events, which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia ≤ 14 days in duration

- Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to Grade < 4 or return to baseline within 7 days.
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Grade 4 drug-related endocrinopathy adverse events (except adrenal insufficiency or hyophysitis) 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 AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued treatment.
- Any new CVA event confirmed by imaging (diffusion-weighted imaging [DWI] MRI preferred unless otherwise contraindicated) regardless of neurological symptoms (e.g. cryptogenic CVA) and for suspected TIA without clear alternative etiology (see Appendix 4).

Tumor assessments should continue as per protocol even if dosing is delayed, and patients must otherwise meet the criteria for continued treatment at the time re-initiation of study therapy is considered.

6.6 Management of Specific Adverse Events

6.6.1 Management Algorithms for Immune-mediated AEs and Cytokine-release Syndrome Associated with Immuno-Oncology Agents

6.6.1.1 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 and product labeling) have been developed to assist Investigators in assessing and managing AEs related to the following organs/systems:

- Gastrointestinal
- Renal

- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Myocarditis
- Neurological

and

- Other immune-mediated AEs (as defined in the nivolumab Investigator's Brochure)

6.6.1.2 Management Algorithm for Cytokine Release Syndrome

Cytokine-release syndrome (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 (ie, 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. For suspected CRS of Grade 3 or above, the Investigator is encouraged to contact the Medical Monitor. An algorithm for the management of CRS is provided in Appendix 6.

6.6.2 Monitoring and Management of Adrenal Insufficiency and Hypophysitis

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

6.6.3 Monitoring and Management of Eosinophilia

6.6.3.1 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.

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.

6.6.3.2 Eosinophilic Disorders

Isolated cases of hypereosinophilic syndrome (HES) and drug reaction with eosinophilia and systemic symptoms (DRESS) 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 Bempegaldesleukin (NKTR-214) Investigator's Brochure.

6.6.4 Treatment of Study Drug-Related Infusion Reactions for NKTR-214/Nivolumab

Infusion reactions have been reported during infusions with NKTR-214 or 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, arthralgia, myalgia, hypotension, hypertension, bronchospasm, or other hypersensitivity/allergic-like reactions. Infusion reactions should be graded as described in Section 9.1.3).

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

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

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

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

- Stop study drug 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.

Consider administration of another dose of diphenhydramine 50 mg IV, remain at the bedside, and monitor the patient until resolution of symptoms.

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before the infusion. If necessary, corticosteroids (up to 25 mg of methylprednisolone or equivalent) may be used.

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

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the patient as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Nivolumab and NKTR-214 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).

6.6.5 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 toxicities 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 6.5.3).

Hepatic events, including elevated liver function tests, have also been observed for nivolumab. Most cases were of low or moderate severity. Higher grade abnormalities are concerning for immune-mediated hepatitis, and typically occur with a later onset (median time to onset of

3.3 months). Immune mediated hepatitis generally results in a quick rise in liver function tests, and responds to corticosteroids or immune-modulating agents. For transaminase elevations occurring in Cycle 2 onwards potentially involving an immune-mediated mechanism, follow the immune-mediated hepatic adverse event management guidelines in the nivolumab Investigator's Brochure for appropriate management.

6.7 Prior and Concomitant Medications

All medications (prescription and over-the-counter [OTC]), vitamin and mineral supplements, and/or herbs taken by the patient from Screening through the 100-day 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) or prophylaxis of an infusion-related reaction should also be included. Recording of prior medications should include prior cancer treatments: previous immunotherapy, chemotherapy, targeted therapy, radiation, OTC medications, herbs, and dietary supplements.

6.7.1 Premedication

Pre-medication with either acetaminophen or ibuprofen for flu-like symptoms can be initiated on either Day 1 or 2 of the dosing cycle and may continue through Day 5 or longer as needed at the discretion of the Investigator.

Pre-medication for rash and/or pruritus with anti-histamines can be initiated on either Day 1 or 2 of the dosing cycle and may continue through Day 5 or longer as needed at the discretion of the Investigator.

6.7.2 Permitted Concomitant Medications

Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Patients with pre-existing adrenal impairment requiring corticosteroid supplementation may be at increased risk for hypotensive episodes during treatment with NKTR-214. For these patients, their existing corticosteroid dose may be increased to adrenal replacement steroid doses > 10 mg of daily prednisone or equivalents for the first 4 days after administration of NKTR-214 based on an assessment of the degree of adrenal impairment and the extent of existing corticosteroid supplementation. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of nonautoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Use of corticosteroids for the management of immune mediated AEs as outlined in the nivolumab Investigator's Brochure is permitted.

Palliative radiation to a symptomatic, solitary lesion may be considered on a case by case basis with approval of the medical monitor. The radiation treatment field may not include a target or measurable lesion by RECIST 1.1.

Administration of vaccines is addressed in Section 6.7.4.

6.7.2.1 Thromboembolism Prophylaxis and Treatment

Patients with a history of a venous or arterial thromboembolic event must be receiving a stable regimen of therapeutic anticoagulation. Anticoagulation options include the following:

- Low molecular weight heparin (LMWH).
- Oral factor Xa inhibitors (direct oral anti-coagulants [DOAC]) such as rivaroxaban, apixaban, or edoxaban).
- Use of warfarin (Coumadin) is permitted; however, therapeutic dosing should target a specific INR stable for at least 4 weeks prior to enrollment. See Section 6.7.3.1.

Unless there is a new medical contraindication observed after Cycle 1 Day 1, a patient with a history of a venous or arterial thromboembolic event must be maintained on therapeutic anticoagulation throughout the patient's participation in the study (i.e., through the EOT visit; see Section 4.1.3).

If anticoagulation is being newly introduced or adjusted, the Investigator may consider consulting the Medical Monitor for guidance.

6.7.3 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 during Days 3 to 8 of each cycle of NKTR-214.

6.7.3.1 Interaction of NKTR-214 and Warfarin

For patients receiving warfarin, therapeutic dosing should target a specific INR that is stable for at least 4 weeks prior to NKTR-214 administration. Because NKTR-214 has the potential to down regulate metabolizing enzymes for warfarin for approximately 1 week after administration of each dose of NKTR-214, frequent monitoring of INR and ongoing consideration of dose adjustments are warranted throughout the patient's participation on study.

6.7.4 Prohibited Concomitant Medications

The following medications are prohibited:

- Immunosuppressive agents such as cyclosporine, tacrolimus, or sirolimus
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.7.2)

- Any antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive nonpalliative radiation therapy, or investigational agent) is prohibited during the study
- Any live/attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose. Note, all vaccines available as of the date of this document against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19) are allowed on treatment. For any questions about COVID vaccines, please contact the Medical Monitor.
- Low dose acetylsalicylic acid (approximately 81 mg/day) should not be combined with LMWH or DOAC due to increased risk of hemorrhage.

6.8 Study Drug Accountability and Reconciliation

NKTR-214 and nivolumab will be supplied globally to the Investigator by Nektar Therapeutics or its designee. Please refer to the Pharmacy Manual for details. At selected sites, commercially available nivolumab may be locally procured with Sponsor approval.

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

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

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

- Records of product delivery, inventory, temperature monitoring, time when drug vial is removed from freezer or refrigerator, 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 STUDY ASSESSMENTS AND PROCEDURES

Assessments for efficacy, [redacted] and PK are described below. See Section 9.0 for safety assessments, including AEs, clinical laboratories, physical examinations, vital signs, and other safety assessments.

7.1 Tumor and Radiographic Assessments

Tumor assessments for all patients will be performed at Screening and every 9 weeks (± 7 days) from Cycle 1 Day 1 for the first 12 months. Beyond 12 months, tumor assessments will decrease in frequency to every 12 weeks (± 7 days). A scan should also be done at EOT (unless a scan was done within the prior 4 weeks). Tumor response will be evaluated using RECIST 1.1 as the primary measure (Section 8.0).

Patients who continue treatment beyond progression should continue to have scans every 9 weeks (± 7 days) for the first 12 months of treatment post-progression and every 12 weeks (± 7 days) in the second year of treatment post-progression (for a maximum treatment duration of 2 years from the beginning of the study).

Patients who discontinue study treatment and do not have BICR-confirmed disease progression should continue to have scans every 90 days (± 10 days) during the follow-up period if clinically feasible, until disease progression is confirmed by BICR. Scans should continue to be collected even if a new antineoplastic regimen has been initiated.

Radiographic assessments (chest/abdomen/pelvis) are required for all patients for tumor measurements. A magnetic resonance imaging (MRI) scan of the brain must be done within 28 days prior to enrollment to determine the presence of CNS metastases at baseline. If the screening brain MRI reveals no evidence of disease follow-up brain imaging does not need to be done on subsequent tumor evaluations unless clinically indicated. Computed tomography (CT) scan of the brain (with contrast) can be performed if MRI is contraindicated or not available. If contrast is contraindicated in the patient, CT of the brain without contrast can be performed. An MRI of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan.

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

The same method of assessment (CT or MRI) and the same technique for acquisition of images must be used for all study assessments (contrast must be used unless medically contraindicated). Radiographic assessments and efficacy analyses will be conducted by the Investigator site as well as independent radiology review.

7.1.1 Central Imaging

Sites should submit all scans to the imaging core laboratory on the schedule outlined in the Study 18-214-10 Imaging Manual, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to 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.

7.2 Pharmacokinetic and Immunogenicity Measurements

Pharmacokinetic and immunogenicity assessment data will be collected from study patients at the time points indicated in Table 3. All time points are relative to the start of NKTR-214 infusion. 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 and immunogenicity sampling should be adjusted accordingly. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. All predose samples should be collected within 24 hours before the start of any dose infusion.

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.

Pharmacokinetic data obtained in this study may be combined with data from other studies in the clinical development program to develop population PK models. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of NKTR-214 and/or nivolumab and to determine measures of individual exposure (such as steady-state peak, trough and time-averaged concentration). Model predicted exposures may be used for exposure response analyses of selected efficacy and safety endpoints. If the analyses are conducted, the results of population PK and exposure response analyses will be reported separately.

Validated methods to detect anti-nivolumab, anti-NKTR-214, anti-PEG, and anti-IL-2 anti-drug antibodies (ADA) will be used to analyze the immunogenicity samples. Immunogenicity sample testing will be done in tiers as per the 2019 FDA guidance (FDA 2019). Samples will be first tested with screening electrochemiluminescence assays (ECLA). Putative positive samples for anti-nivolumab, anti-NKTR-214, or anti-IL-2 ADA will then be analyzed in competition ECLA

to confirm positivity. Confirmed anti-NKTR-214 ADA positive samples will be tested further in a PEG immunocompetition assay to determine the antibody specificity of the reactivity to the PEG or non-PEG (IL2, linker) moiety of NKTR-214. Confirmed positive samples from anti-nivolumab, anti-NKTR-214, and anti-IL2 ADA assays will then be tested to obtain a titer. Samples confirmed to be positive for anti-nivolumab, anti--NKTR-214, and anti-IL2 ADA may also be tested for neutralizing activity for IL-2 and nivolumab using validated cell-based assays.

PK samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. Blood samples from PK or biomarker assessment may also be used for immunogenicity analysis if required (e.g., insufficient volume for complete immunogenicity assessment or to follow-up on suspected immunogenicity related AE).

For all PK blood samples, the date and actual time of collection 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.

Depending on the ability to process these samples, storage facilities, or availability of courier pickup/dry ice, individual sites may opt out of these PK and immunogenicity assessments.

Table 3: Pharmacokinetic, Immunogenicity, [redacted] Sampling Schedule

Study Cycle/Day Cycle = every 3 weeks	Event (Relative to Start of NKTR-214 Infusion)	Time (Relative to Start of NKTR-214 Infusion) Hour:Min	NKTR-214 Blood Samples		Nivolumab Blood Samples		[redacted]
			PK[e]	IMG	PK	IMG	
Cycle 1 Day 1	Predose[a]	00:00	X	X	X	X	
	End of infusion[b]	00:30	X				
		04:00[c]	X				
Cycle 1 Day 3		48:00[c]	X				
Cycle 1 Day 5		96:00[d]	X				
Cycle 1 Day 8		168:00[d]	X				
Cycle 2 Day 1	Predose[a]	00:00	X	X	X	X	
Cycle 5 Day 1	Predose[a]	00:00	X	X	X	X	
Cycle 8 Day 1	Predose[a]	00:00					
Cycle 11 Day 1	Predose[a]	00:00	X	X	X	X	
Cycle 17 Day 1	Predose[a]	00:00	X	X	X	X	
Cycle 25 Day 1	Predose[a]	00:00	X	X	X	X	
Cycle 33 Day 1	Predose[a]	00:00	X	X	X	X	
Follow-up 30 Day				X	X	X	
Follow-up 100 Day				X	X	X	

IMG = immunogenicity; PK = pharmacokinetic

a. Predose samples should be collected within 24 hours before the start of any dose infusion.

b. The end of infusion sample should be taken immediately prior to stopping the NKTR-214 infusion (preferably within 2 minutes prior to the end of infusion). End of infusion samples may not be collected from the same IV access as drug was administered. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

c. Time window for 4-hour sample is ± 1 hour; time window for 48-hour samples is -1 day (i.e., 24 to 48 hours)

d. Time window for Day 5 and Day 8 sample is ± 1 day

e. The NKTR-214 PK blood samples will also be used [redacted]

7.3 PD-L1 Assay

Baseline tumor samples will be collected for central analysis utilizing the PD-L1 IHC 22C3 pharmDx assay. This is a companion diagnostic to select patients with locally advanced or metastatic urothelial carcinoma who are cisplatin-ineligible for treatment with pembrolizumab. This assay is a qualitative immunohistochemical assay using monoclonal mouse anti-PD-L1, clone 22C3 for the detection of PD-L1 protein in FFPE tissues using EnVision FLEX visualization system on Autostainer Link 48 (Dako North America Inc., 2018). PD-L1 protein expression in urothelial carcinoma is determined by using CPS, which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen should be considered to have low PD-L1 expression if CPS < 10. The specimen should be considered to have high PD-L1 expression if CPS ≥ 10. Samples that have < 100 evaluable cells are considered not evaluable.

The clinical validity of PD-L1 IHC 22C3 pharmDx in evaluating PD-L1 expression in patients not eligible for cisplatin-containing chemotherapy with locally advanced or metastatic urothelial carcinoma is based on the pembrolizumab Keynote-052 study. Thirty percent of enrolled patients (110 of 370) had tumors that expressed PD-L1 with a CPS of greater than or equal to 10 (CPS ≥ 10) and 70% (251 of 370) had a CPS less than 10 (CPS < 10) (Agilent Technologies, Inc., 2018).

7.5 Tumor Tissue Specimens

A fresh tumor biopsy must be provided during Screening. The following biopsy types are allowed:

- core biopsy
- punch biopsy
- excisional biopsy
- surgical specimen

Biopsies should be performed on lesions that have not been exposed to prior radiation. Tumor lesions used for biopsy should not be classified as target lesions, unless there are no other lesions suitable for biopsy.

The following are not acceptable for submission:

- Fine needle biopsies
- Biopsies of bone lesions that do not have a soft tissue component.

Sufficient, recent tumor tissue FFPE block or minimum of 10 unstained slides, preferably 15 to 25 slides, obtained within 12 months prior to enrollment from a metastatic tumor lesion or from an unresectable primary tumor lesion, which has not been previously irradiated, may be submitted in lieu of fresh tissue. Patients should not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained. Please obtain consent to access archival tumor tissue. These biopsy samples are sent directly to a sponsor designated central lab for PD-L1 testing.

An optional on-treatment tumor tissue sample will be collected prior to Cycle 2 Day 1, on Days 14 to 21 of Cycle 1 (Table 4). This on-treatment biopsy is optional but highly recommended. An optional tumor biopsy will also be collected upon recurrence when safe and feasible. These optional biopsies should only be performed if they can be safely obtained. The assessment of the risk to the patient lies solely with the treating physician. These samples may be used for the assessment of markers implicated in resistance to immunotherapeutic agents,

including but not limited to other CD8+ T-cell checkpoint receptors and ligands (e.g., Lag-3, Tim-3), mutations in cancer related genes, and intratumoral immune cell subsets, including but not limited to, Tregs and myeloid derived suppressor cells (MDSCs). [redacted] Both the pre-treatment tumor sample and the sample collected on-treatment and upon recurrence may be retrospectively assessed for the expression of other immune or urothelial carcinoma related genes, RNAs and/or proteins, or for the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to IHC, qRT-PCR, genomics, genetic mutation detection, and fluorescent in-situ hybridization.

Table 4: Tumor Biopsy Sampling Schedule

Collection Timing	Tumor Biopsy
Screening	X[a]
Cycle 1 Days 14-21[b]	X
Upon progression[b]	X

a. Unstained formalin-fixed paraffin-embedded (FFPE) tumor tissue sections on slides (minimum of 10, preferably 15 to 25) or a FFPE tumor tissue block, collected within 12 months prior to enrollment and without intervening therapy, are acceptable in lieu of a fresh tumor biopsy prior to treatment.
b. Sample collection is optional but highly recommended.

7.5.1 Tumor Mutation Burden

Tumor mutation burden (TMB) refers to the total number of nonsynonymous somatic mutations that exist within a tumor's genome. A subset of these mutations, termed neo-antigens, may result in an expressed protein that is not recognized by the host's immune system as self, and therefore has the potential to be immunogenic, leading to an anti-tumor immune-mediated response. Tumors with a high mutation burden may have a higher rate of neo-antigens that, in principle, would be expected to be more immunogenic than tumors with comparatively low mutation burden (Goodman, 2017). Therefore, high TMB has been hypothesized to correlate with improved efficacy in patients treated with immuno-oncology therapies. This hypothesis has been supported in multiple publications across immuno-oncology therapies, tumor types, and lines of treatment. Published studies of TMB as a biomarker of clinical outcomes was reported by Snyder, 2014, 2017, where high TMB was found to be associated with efficacy in UC and melanoma patients treated with anti-CTLA-4 therapy. Further studies by Rizvi, 2015 reported TMB as a biomarker of pembrolizumab efficacy in second-line NSCLC patients and nivolumab plus ipilimumab efficacy in 1L NSCLC patients (Hellmann, 2018).

The recent study of atezolizumab in platinum-treated locally advanced or metastatic UC also suggests high TMB is associated with improved response. TMB was also evaluated in post hoc

analysis in the BMS-sponsored second-line UC Phase 2 CheckMate 275 study. The results demonstrated that high TMB was significantly associated with higher ORR, longer PFS, and longer OS in patients treated with nivolumab (Galsky, 2017). Moreover, patients with high TMB derived benefit from nivolumab across tumor PD-L1 expression levels.

7.6 Sample Collection and Storage

This protocol will include residual sample storage for additional research.

All requests for access to samples or data for additional research will be vetted through a diverse committee of the Sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

Additional research is optional for all study patients, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational research and development capability at the Sponsor, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. [redacted]

Samples kept for future research will be stored at the Sponsor's Biorepository or an independent, Sponsor-approved storage vendor. The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 15 years after the end of the study or the maximum allowed by applicable law. Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the Laboratory Manual.

7.7 Health-Related Quality of Life (HRQoL)

The evaluation of health-related quality of life (HRQoL) 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 HRQoL measures provide data needed for calculating utility values to inform health economic models. At each visit specified in Table 3, prior to any other study assessments, HRQoL will be assessed.

Patients will be asked to complete the 3-level version of the EuroQol Group's EQ-5D (EQ-5D-3L) and EORTC Quality of Life Questionnaire (QLQ-C30) during screening, after enrollment but prior to first dose, at on-study clinic visits occurring every 3 weeks while on treatment, and at Follow-up Visits 1 and 2. In addition, the EQ-5D-3L will be completed via telephone during the survival follow-up phase. The FACIT GP5 is not required to be performed at the Screening visit. FACIT GP5 must be performed after dosing on Cycle 1 Day 1; at all other study visits specified in Table 3, FACIT GP5 should be performed prior to any other study assessments.

The questionnaires will be provided in the patient's preferred language. There exists a standardized guide that can be used to facilitate telephone administration of the EQ-5D-3L. Additional information regarding each test can be found below.

7.7.1 FACIT GP5

A single item, FACIT GP5, from the Functional Assessment of Cancer Therapy - General (FACT-G), will be used to assess the extent of perceived bother due to symptomatic adverse events. Evidence exists for the validity of this item and its usefulness as an overall summary measure of burden due to symptomatic treatment toxicities (Pearman, 2018). The item is rated on a 0 (not at all) to 4 (very much) Likert type scale.

GP5 uses a recall period of the past 7 days.

7.7.2 EORTC QLQ-C30

The EORTC QLQ-C30 (Aaronson, 1993) is the most commonly used quality of life instrument in oncology trials. The instrument's 30 items are divided among five functional scales (physical, role, cognitive, emotional, and social), nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health/quality of life scale. With the exception of two items included in the global health/quality of life scale, for which responses range from 1 (very poor) to 7 (excellent), item responses range from 1 (not at all) to 4 (very much). Raw scores for the QLQ-C30 are transformed to a 0–100 metric such that higher values indicate better functioning or QoL or a higher level of symptoms.

The QLQ-C30 uses a recall period of the past week.

7.7.3 EQ-5D-3L

The 3-level version of the EQ-5D (EQ-5D-3L) (EuroQol Group, 1990) will be used to assess treatment effects on perceived health status and to generate utility data for health economic evaluations. The EQ-5D-3L is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 3 levels: no problems, some problems, and severe problems.

Responses to these 5 dimensions are converted into 1 of 243 unique EQ-5D health state descriptions, which range between no problems on all 5 dimensions (11111) to severe/extreme problems on all 5 dimensions (33333). Using appropriate country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility index representing the societal desirability of his or her own health. In addition, the EQ-5D includes a visual analogue scale (VAS) allowing a respondent to rate his/her health on a scale ranging from 0–100 with 0 being the worst health state imaginable and 100 being the best health state imaginable. The EQ-5D-3L uses a recall period of today.

8.0 ASSESSMENT OF EFFICACY

Response and progression will be determined by blinded independent radiology review using RECIST 1.1 (Eisenhauer, 2009). Investigator assessed response will also be done according to RECIST 1.1.

Patients will be assessed for response by CT or MRI every 9 weeks (± 7 days) for the first 12 months and every 12 weeks (± 7 days) until progression or treatment discontinuation, whichever occurs later (see Section 7.1). A scan should also be done at EOT (unless a scan was done within the prior 4 weeks).

Patients who continue treatment beyond progression should continue to have scans every 9 weeks (± 7 days) for the first 12 months of treatment post-progression and every 12 weeks (± 7 days) in the second year of treatment post-progression (for a maximum treatment duration of 2 years from the beginning of the study).

Patients who discontinue study treatment and do not have BICR-confirmed disease progression should continue to have scans every 90 days (± 10 days) during the follow-up period if clinically feasible, until disease progression is confirmed by BICR. Scans should continue to be collected even if a new antineoplastic regimen has been initiated.

8.1 Definitions

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

8.1.1 Measurable Disease

Target tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm); when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

8.1.2 Nonmeasurable Disease

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes ≥ 10 to < 15 mm in short axis) as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, or

abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by reproducible imaging techniques.

8.2 Specifications by Methods of Measurements

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

8.2.1 Clinical Lesions

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

8.2.2 CT, MRI

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

8.2.3 Tumor Markers

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

8.2.4 Cytology, Histology

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

8.3 Tumor Response Evaluation

8.3.1 Assessment of Overall Tumor Burden at Baseline and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least 1 measurable lesion.

8.3.2 Baseline Documentation of 'Target' and 'Nontarget' Lesions

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

Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for nonnodal 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 nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.'

8.3.3 Special Notes on the Assessment of Target Lesions

8.3.3.1 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. For PR, stable disease, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

8.3.3.2 Target Lesions That Become 'Too Small to Measure'

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

8.4 Response Criteria Using RECIST 1.1

8.4.1 Evaluation of Target Lesions

Table 5 provides the definitions of the criteria used to determine objective tumor response for target lesions. CR and PR should be confirmed 4 weeks after the initial scan.

Table 5: Criteria to Determine Objective Tumor Response for Target Lesions per RECIST 1.1

Criteria	Definition
Complete Response (CR)	• Disappearance of all target lesions Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial Response (PR)	• At least a 30% decrease in the sum of the longest diameters (SLD) of target lesions, taking as reference the baseline SLD. For lymph nodes (target lesions) the actual short axis measurement should be recorded (measured in the same anatomical plane as the baseline examination).
Progressive Disease (PD)	At least a 20% increase in the SLD of target lesions, taking as reference the smallest SLD on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm relative to nadir. Note: the appearance of 1 or more new lesions is considered progression.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

8.4.2 Evaluation of Nontarget Lesions

Table 6 provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. Although some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points of radiographic assessments.

Table 6: Criteria to Determine Tumor Response for Nontarget Lesions per RECIST 1.1

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

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

a. In this setting, when a patient has measurable disease, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in the nontarget disease such that, even in the presence of stable disease or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of stable disease or PR of target disease will therefore be extremely rare (from Section 4.3.4 of RECIST 1.1).

8.4.3 Duration of Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

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.

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

8.5 Blinded Independent Central Review

Radiographic images will be collected for BICR. Details for the analyses are described in the imaging core laboratory charter.

9.0 ASSESSMENT OF SAFETY

9.1 Adverse Events

9.1.1 AE Definition and Assessment

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

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

An AE does not include:

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

9.1.2 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). All 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 9.2.2).

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.

9.1.3 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) CTCAE v 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.

9.1.4 Causality Relationship of AEs

The relationship of each AE to each study drug (NKTR-214 or nivolumab, or both) 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 medical history, preexisting medical condition, underlying disease, concurrent illness, or concomitant medications/therapies.

- Possibly related: The AE may be related to the investigational agent(s). A plausible temporal sequence exists between the time of administration of the investigational product and the development of the AE, and it follows a known response pattern to the investigational product. The reaction may have been produced by the patient's clinical state or other concomitant therapies or interventions.
- Related: The AE is clearly related to the investigational agent(s). A plausible temporal sequence exists between the time of administration of the investigational product and the development of the AE, and it follows a known response pattern to the investigational product. The occurrence of this AE can be confirmed with a positive re-challenge test or supporting laboratory data.

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

9.1.5 AE Reporting and Follow-up

After initiation of study drug treatment, all AEs will be reported from the time of first study drug(s) administration until 100 days after the last dose of all study drug(s). For SAEs, additional reporting requirements also apply (see Section 9.2.2).

All ongoing AEs will be followed until resolution, the patient is lost to follow-up, patient death, or until the Follow-Up Visit 2, whichever is earlier. In case the AE has not completely resolved by the Follow-Up Visit 2, 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 9.2.1 and 9.2.2.

9.2 Serious Adverse Events

9.2.1 SAE 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 (for ≥ 24 hours) 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 hospitalizations for social reasons or due to long travel distances or for prophylactic patient observation), in the absence of an AE.

- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed above.

Death is an outcome of an AE and not an AE in itself. All events leading to death, regardless of relationship to study drugs, that occur during the protocol-specified reporting period, must be reported with the exception of deaths attributed to disease progression (refer to Section 9.3). 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.

9.2.2 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, with an onset within 100 days after the last dose of all study drug(s) will be reported to Nektar Therapeutics Drug Safety immediately without undue delay, under no circumstances later than 24 hours following knowledge.

In addition, all SAEs that are assessed by the Investigator as related to study drug(s) and occurring after the SAE reporting period will also be reported to Nektar Therapeutics Drug Safety immediately without undue delay, under no circumstances later than 24 hours following knowledge.

SAEs must be reported to Nektar Therapeutics Drug Safety via email or 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 Fax as a backup system should there be EDC system access issues.

The Investigator must complete the SAE Report Form, assess the causality relationship to the study treatment as applicable, and send the completed SAE form via email or fax to Nektar Therapeutics Drug Safety. A follow-up report and any additional records (such as hospital records, consultant reports, and autopsy findings) will be emailed or faxed to Nektar Therapeutics Drug Safety immediately without undue delay, under no circumstances later than 24 hours following knowledge. Any medication or other therapeutic measures used to treat the event will be recorded.

All SAEs will be followed as described in Section 9.2.3.

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.

9.2.3 Serious AE Follow-up

All study treatment-related SAEs that have not resolved by the EOT visit (Section 4.1.3) 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 Follow-up Visit 2 (Section 4.1.3), whichever is earlier. In the case where an unrelated SAE has not completely resolved by the Follow-up Visit 2, the final outcome of these ongoing unrelated SAEs will be captured as “Not Recovered/Not Resolved” or “Recovering/Resolving,” whichever is applicable.

9.3 Disease Progression – Not Reportable as an AE

It is anticipated that during this study a proportion of patients will experience disease progression prior to study discontinuation. 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 clinical manifestations may be reported as non-fatal SAEs.

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

- Seriousness Criteria = Cannot equal to Death
- Severity = Cannot equal to 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.

9.4 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 imAEs.

See Section 6.6.1 for additional information on management algorithms for immune-mediated AEs.

9.5 Additional Information Collected for Adverse Events Primarily Related to NKTR-214

Additional information may also be collected on select AEs primarily related to NKTR-214 (eg, capillary leak syndrome and CRS).

9.6 Adverse Events of Special Interest

CVA events (any grade) are considered AESI and should be classified as serious or non-serious following the standard seriousness definition. However, all CVAs are required to follow the timeline for SAE reporting (within 24 hours as described in Section 9.2.2) from the sites to Nektar Drug Safety: pharmacovigilance@nektar.com. CVA Management Guidelines are provided in Appendix 4.

9.7 Pregnancy Tests/Pregnancy

9.7.1 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 3) 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 9.7.2.

9.7.2 Pregnancy

9.7.2.1 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 after the last dose of NKTR-214 or nivolumab 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 9.2.2. 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.

9.7.2.2 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 13.2).

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 9.2.2. 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.

9.8 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 9.2.2 for reporting details). Potential DILI is defined as:

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

AND

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

AND

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

9.9 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Section 9.2.2). All instances of accidental overdose and/or dosing errors should be reported on the Dosage Administration Record eCRF.

9.10 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 has provided 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.

9.11 Clinical Laboratory Tests

Clinical laboratory samples will be collected according to the Schedule of Events (Table 1). Clinical laboratory tests will be performed by a central laboratory, with the exception of pregnancy testing which will be done locally. A list of the clinical laboratory analytes to be tested is provided in Appendix 2A. In cases of a safety concern, blood samples may be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. For enrollment, if the central laboratory tests are cancelled, lost, or considered inadequate for analysis, the site may forward an identical set of local laboratory samples for eligibility review (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, enrollment may proceed. Additional clinical laboratory tests may be ordered at the Investigator's or qualified Sub-Investigator's discretion.

The Investigator or qualified Sub-Investigator must review all laboratory results for clinical significance and document their review. 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 9.1.

9.12 Physical Examinations

Physical examinations should be conducted according to the Schedule of Events (Table 1). Full physical examinations should be conducted at screening, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Focused physical examinations will be done at Day 1 of each cycle and during the follow-up period. Focused physical examinations are at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be reported at each visit for dosing of NKTR-214/nivolumab (ie, on the day of dosing and not earlier), height at screening visit only. Other examinations are to be performed as clinically

indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious AE page.

9.13 Vital Signs

Vital sign measurements will be recorded according to the Schedule of Events (Table 1). Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation by pulse oximetry (oxygen saturation on dosing days only), and temperature. It is preferred that the same arm be used for all blood pressure readings, if possible. Pre dose on Cycle 1 Day 1 and on Cycle 1 Day 3 orthostatic blood pressure measurement should be completed. This involves taking a blood pressure measurement while the patient is supine after 5 minutes of rest and a second blood pressure measurement within 2 to 5 minutes of the patient standing. Instructions for more frequent vital sign monitoring after completion of study drug administration are provided in Section 6.2.1.

9.14 Electrocardiograms

A 12-lead ECG will be recorded at Screening only, within 14 days of Day 1.

9.15 Echocardiograms

Patients must have a documented LVEF > 45% using standard echocardiogram or MUGA scan test within 60 days prior to Cycle 1 Day 1. Echocardiograms done as standard of care may be used if they meet the above criteria (Table 1).

10.0 STATISTICAL PLAN

10.1 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.

A detailed description of analysis methods will be provided in the statistical analysis plan (SAP). The potential impact of COVID-19 on this trial will be assessed. Any changes to the analyses that are required due to COVID-19 will be detailed in the SAP.

10.2 Determination of Sample Size

The original protocol planned to enroll approximately 185 patients to receive NKTR-214 and nivolumab. Amendment 2.0 added a GemCarbo arm and reduced the overall number of patients planned to approximately 165 (110 to receive NKTR-214/nivolumab, 55 to receive GemCarbo). Amendment 3.0 eliminated the GemCarbo arm after 2 patients had enrolled in this arm, and modified the overall planned number of NKTR-214/nivolumab patients to 175. With Amendment 5.0, enrollment is complete at 2 patients who received GemCarbo and 190 patients who received NKTR-214/nivolumab.

The study will evaluate the totality of the data including DOR, and ORR, and CR rate.

Although this study is enrolling both PD-L1 low and PD-L1 high expressors in an unselected fashion, the sample size was determined by the PD-L1 low population. Review of available urothelial carcinoma-specific PD-L1 data suggest that approximately 70% of patients have PD-L1 low tumors, while 30% have PD-L1 high tumors using the PD-L1 IHC 22C3 pharmDx assay (pembrolizumab) (CPS ≥ 10) (Vuky, 2018; KEYTRUDA® Prescribing Information, 2018; TECENTRIQ® Prescribing Information, 2018).

This trial will enroll at least 110 patients who have tumors that are PD-L1 low. The null hypothesis is that the ORR is ≤ 21%. The alterative hypothesis is that the ORR is > 21%. The null hypothesis was based on the Keynote-052 study of 1L pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic UCC; in that study, ORR was 20.3% in patients with PD-L1 CPS < 10 (Vuky, 2020).

Assuming an ORR rate of at least 34%, with at least 110 patients, the study will have more than 82% power to demonstrate that the lower limit of the 95% two-sided confidence interval (CI) for ORR exceeds 21%, where the CI is calculated by the exact computation method.

10.3 Analysis Sets

Treated PD-L1 Low Population: All PD-L1 low patients who receive at least 1 dose (or partial dose) of NKTR-214/nivolumab or GemCarbo. The cut-off point defining low PD-L1 expression

will be CPS < 10 (see Section 7.3). This is the analysis set for all efficacy and safety analyses in PD-L1 low patients, as well as, corresponding demographics, baseline characteristics, and study drug administration.

Treated PD-L1 High Population: All PD-L1 high patients who receive at least 1 dose (or partial dose) of NKTR-214/nivolumab or GemCarbo. Patients with CPS ≥ 10 will be considered to have high PD-L1 expression and will be referred to as high PD-L1 patients (see Section 7.3). This is the analysis set for all efficacy and safety analyses in PD-L1 high patients, as well as, corresponding demographics, baseline characteristics, and study drug administration.

Treated Population: All patients who receive at least 1 dose (or partial dose) of NKTR-214/nivolumab or GemCarbo. This is the analysis set for all efficacy and safety analyses in all NKTR-214/nivolumab or GemCarbo treated patients, as well as, corresponding demographics, baseline characteristics, and study drug administration.

GemCarbo Population: All patients who were randomized to receive at least 1 dose (or partial dose) of GemCarbo per a prior study amendment. This is the analysis set for all analyses in all GemCarbo treated patients, as well as, corresponding demographics, baseline characteristics, and study drug administration.

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

[redacted]

10.4 Demographics and Baseline Characteristics

Demographic data (age, sex, ethnicity, body weight) and baseline disease characteristics will be tabulated, summarized, and presented in data listings.

10.5 Efficacy

10.5.1 Primary Analysis

ORR is defined as the percentage of patients with a confirmed best overall response of CR or PR by RECIST 1.1 per BICR. The ORR and its corresponding 95% exact CI will be calculated by the Clopper-Pearson method. The primary analysis will be performed approximately 18 months after the last patient has been enrolled into the study. The complete response rate will be summarized similarly to ORR.

The best overall response is the best response recorded from the start of the treatment until first occurrence of disease progression or recurrence (taking as reference for progressive disease the

smallest measurements recorded since the treatment started) or the start of a new anticancer therapy.

10.5.2 Secondary Analyses

10.5.2.1 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 RECIST 1.1 to the date of the documentation of disease progression as assessed by BICR or death due to any cause, whichever is earlier. Patients who do not have disease progression or die will be censored on the date of their last evaluable tumor assessment. The median DOR will be estimated using the Kaplan-Meier method with corresponding 95% CI and range. DOR by Investigator assessment will be a sensitivity analysis.

The last evaluable tumor assessment is defined as the last scan before initiation of any anti-cancer therapies and with a response of CR, PR, stable disease, or PD measured by RECIST 1.1.

[redacted]

10.5.3.2 Overall Survival

OS is defined as the time between the date of first dose 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 Kaplan-Meier method will be used to summarize OS, similar to PFS. The OS rates at 6 and 12 months will also be estimated.

10.6 Safety

All safety data will be summarized using descriptive statistics. 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 laboratory parameters, including hematology, chemistry, liver function, and renal function, will be summarized using worst grade NCI CTCAE v 5.0 criteria.

10.6.1 Study Drug Exposure

A patient's extent of exposure to NKTR-214 and nivolumab, generated from the study drug administration eCRF, will be summarized by treatment arm.

10.6.2 Adverse Events and Laboratory Evaluations

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA). All TEAEs, treatment-related AEs, SAEs, and treatment-related SAEs will be summarized using the worst grade per NCI CTCAE v 5.0 by system organ class and preferred term.

A TEAE is defined as: (regardless of intensity):

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

A separate listing and summary of all imAEs will be provided. A listing and summary of patients who discontinued study drug(s) due to an AE will be provided.

Vital signs (including change in weight) and clinical laboratory test results will be summarized descriptively. Data and change from baseline at all scheduled time points will be tabulated.

A data listing for all deaths will be provided.

10.6.3 Other Safety Evaluations

Any significant physical examination findings will be listed.

All reported prior and concomitant medications will be mapped using the World Health Organization Drug Dictionary, and tabulated in summary tables and data listings. Individual data for medical history will also be listed and summarized descriptively as appropriate.

10.7 Pharmacokinetics

Plasma concentrations of NKTR-214 and its metabolites, and serum nivolumab concentrations, will be measured. Pharmacokinetic parameters such as C_{max}, T_{max}, AUC, clearance (CL), volume of distribution (V_d), and half-life ($t_{1/2}$) will be estimated from concentration-time data where possible. Pharmacokinetic data from this study may also be pooled with data from other clinical studies for the purpose of PK modeling. Pharmacokinetic parameters will be tabulated and

summarized using descriptive statistics. Select PK parameter values will be correlated with select safety and response measurements for assessment of exposure-response relationships. Data from patients prematurely ending participation in the study may be excluded from the PK data evaluation.

10.8 Health-Related Quality of Life (HQRoL)

Patient-reported outcome (PRO) measures include EORTC QLQ-C30, FACIT GP5, and EQ-5D-3L. Summary statistics for PRO measures at each assessment point will be provided. The mean change from baseline will also be reported at each post-baseline assessment point.

[redacted]

10.10 Missing Data

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

10.11 Independent Data Monitoring Committee (IDMC)/Sponsor Executive Committee (SEC)

This study was monitored by an IDMC, comprised of qualified clinicians and a biostatistician all independent from Nektar Therapeutics and investigational sites, selected to avoid conflict(s) of interest. The IDMC reviewed data from the first 20 patients who received at least 2 cycles of NKTR-214 and nivolumab.

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

Following the initial IDMC review on safety and other relevant data, the reviews are continued by a Sponsor Executive Committee (SEC) consisting of Nektar's Chief Medical Officer, Head of Data Science and Systems, and Head of Regulatory Affairs, none of whom are directly involved in study conduct. In addition to the Medical Monitor's routine review of safety, the SEC will formally review ongoing safety at 6-month intervals.

11.0 STUDY OR STUDY SITE TERMINATION

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

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

12.0 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.

12.1 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, 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.

12.2 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, and local regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) for the patients in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor. The Investigational New Drug Application (IND) regulations and ICH E6 guidelines also require the Investigator to allow authorized representatives of the Sponsor, IRB/IEC, FDA, and other relevant regulatory authorities direct access to study source records, and to inspect and make copies of the same records. The names and identities of the patients need not be divulged to the Sponsor; however, the records must nevertheless be available to be inspected for review. This can be accomplished by blacking out the patient's name and replacing the name with the patient's study identification number. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the Investigator must inform the Sponsor of these restrictions before initiation of the study.

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

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

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

13.0 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 the current ICH GCP guidelines (ICH E6), as well as with any applicable regulatory authority, federal, state and/or local laws and regulations.

13.1 IRB/IEC Approval

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

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

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

13.2 Written Informed Consent

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

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

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. For the Sponsor or designee to collect any pregnancy surveillance information, the pregnant patient or partner must sign an informed consent form for disclosure information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

14.0 DATA HANDLING AND RECORD KEEPING

14.1 Data Collection Instruments and Source Documents

14.1.1 Study Records

During the study, the Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study 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 study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 section 8.0) and as required by the applicable regulatory requirement(s). The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

14.1.2 Data Collection Instruments

Data collection instruments (DCIs) (e.g., electronic CRFs [eCRFs] 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. Nektar, representatives of Nektar, and investigational sites will have access to the study data. Study data will be stored in a validated, access-controlled, password-protected database.

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.

14.2 Retention of Essential Documents

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

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

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

14.3 Confidentiality

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

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 by Interactive Response Technology (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. Exact date of birth and patient name/initials are not collected.

The study site is not to provide any personal data relating to patient from Study Data that will be transferred to Nektar. Only the study site will be able to connect the patient identification number a patient’s personal data.

14.4 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.

15.0 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: ECOG PERFORMANCE STATUS CRITERIA

0 Fully active; able to carry on all pre-disease performance without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours

3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours

4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

5 Dead

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55

APPENDIX 2: CLINICAL LABORATORY TESTS

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

- Appendix 2A: Table of the laboratory tests performed in this study
- Appendix 2B: Table of the local laboratory tests to be obtained prior to study drug dosing

APPENDIX 2A: LABORATORY TESTS PERFORMED IN THIS STUDY

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Chemistry</th><th>Serology</th></tr>
<tr><td>• Hemoglobin (Hgb)
• Hematocrit (HCT)
• Platelet count
• White blood cell (WBC) count
• Neutrophils
• Lymphocytes
• Monocytes
• Eosinophils
• Basophils</td><td rowspan="3">• AST (SGOT)
• ALT (SGPT)
• Alkaline phosphatase (ALP)
• Albumin
• Creatinine
• Calculated creatinine clearance
• Calcium
• Creatine kinase
• 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</td><td>• Hepatitis B surface antigen (HBsAg)
• Hepatitis C virus antibody (anti-HCV)
• Human immunodeficiency virus (HIV) antibody</td></tr>
<tr><th>Coagulation</th><th>Additional Labs</th></tr>
<tr><td>• Partial thromboplastin time (PTT)
• Prothrombin time (PT)</td><td>• Serum or urine pregnancy (HCG) for WOBCP
• FSH[a]
• Thyroid stimulating hormone (TSH)
• Free thyroxine (T4)
• Free or total triiodothyronine (T3)
• Lipase
• Amylase
• C-reactive protein (Screening only)</td></tr>
<tr><th colspan="3">Urinalysis</th></tr>
<tr><td colspan="2">• Specific gravity
• pH
• Glucose
• Protein
• Bilirubin
• Ketones
• Leukocyte esterase
• Blood
• Creatinine</td><td>For positive protein, white blood cell or blood, a microscopic examination including:
• Red blood cells
• White blood cells
• Epithelial cells
• Bacteria
• Crystals
• Casts</td></tr>
</table>

WOCBP = women of childbearing potential

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 3).

APPENDIX 2B: LOCAL CLINICAL LABORATORY TESTS OBTAINED PRIOR TO STUDY DRUG ADMINISTRATION

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

WOCBP = women of childbearing potential

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

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

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal 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 level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PATIENTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration for female patients and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment for female patients treated with NKTR-214/nivolumab or 6 months after the end of study treatment for female patients who received GemCarbo on a prior protocol amendment.*

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 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*
• 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)
* Local laws and regulations may require use of alternative and/or additional contraception methods.

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the Investigator.
- Male patients are required to use a condom for study duration and until end of relevant systemic exposure defined as 3 months after the last dose of NKTR-214 for male patients treated with NKTR-214/nivolumab or 6 months after the end of study treatment for male patients who received GemCarbo on a prior protocol amendment.
- 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 male patients treated with NKTR-214/nivolumab or 6 months after the end of study treatment for patients who received GemCarbo on a prior protocol amendment.
- 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 for male patients treated with NKTR-214/nivolumab or 6 months after the end of study treatment for male patients who received GemCarbo on a prior protocol amendment.
- Refrain from donating sperm for the duration of the study treatment and until 3 months after the last dose of NKTR-214 for male patients treated with NKTR-214/nivolumab or 6 months after the end of study treatment for male patients who received GemCarbo on a prior protocol amendment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.7 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 4: CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM

Table 7 provides a management algorithm for possible signs/symptoms of CVA for patients treated with the combination of NKTR-214 with a checkpoint inhibitor. 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.

Table 7: Cerebrovascular Accident Adverse Event Management Algorithm

For unexplained neurological symptoms (such as hemiparesis, confusion, dysarthria, or visual disturbances) that may be associated with CVA: **perform neurological imaging with MRI including diffusion-weighted imaging (DWI) as soon as feasible after initial presentation of symptoms (preferably within 24 hours).** DWI MRI is preferred, but if contraindicated, alternative imaging modalities may be used. If imaging is consistent with a CVA, proceed to the following:	
1	For any new CVA event confirmed by imaging (DWI MRI preferred unless contraindicated), regardless of neurological symptoms (eg, cryptogenic CVA), and for suspected TIA without clear alternative etiology: • Discontinue study treatment for patients receiving NKTR-214 in combination with a checkpoint inhibitor (ie, nivolumab).
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.

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

APPENDIX 5: GUIDELINES FOR PATIENTS RANDOMIZED TO GEMCITABINE/CARBOPLATIN (GEMCARBO) TREATMENT IN AN EARLIER PROTOCOL VERSION

Note: The GemCarbo arm is no longer applicable at Amendment 3 and beyond.

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1.0 SCHEDULE OF EVENTS FOR PATIENTS PREVIOUSLY RANDOMIZED TO GEMCITABINE/CARBOPLATIN (GEMCARBO)

Appendix 5, Table 1: Schedule of Events for Patients Previously Randomized to GemCarbo (Excluding Pharmacokinetic, Immunogenicity, [redacted] Sampling)

Procedure / Period:	Screening	Treatment								Post-treatment				
		Cycle 1 Only					Cycle 2 and Beyond			EOT[q]	Cross Over	Follow-up[s]		Survival Follow-up[t]
						GemCarbo Arm Only		GemCarbo Arm Only						
Study Days[a]:	Day -28 to -1	Day 1	Day 3 (- 1 day)	Day 8 (± 3 days)	Days 14-21	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 8 (± 3 days)	Day 15 (± 3 days)	(±7 days)	Rescreening[r]	30 days from last dose (± 7 days)	100 days from last dose (± 7 days)	Every 3 months (± 14 days)
Informed consent	X										X			
Inclusion/ exclusion criteria	X										X			
Medical history	X										X			
Physical examination[b]	X	X		X			X			X	X	X	X	
Vital signs[c]	X	X		X			X			X	X	X	X	
ECOG performance status[d]	X	X					X			X	X	X	X	
ECG[e]	X										X			
ECHO/MUGA[f]	X										X			
Pregnancy test[g]	X	X					X			X	X	X	X	

Appendix 5, Table 1: Schedule of Events for Patients Previously Randomized to GemCarbo (Excluding Pharmacokinetic, Immunogenicity, and Biomarker Sampling) (Contd)

Procedure / Period:	Screening	Treatment								Post-treatment				
		Cycle 1 Only					Cycle 2 and Beyond			EOT[q]	Cross Over	Follow-up[s]		Survival Follow-up[t]
						GemCarbo Arm Only		GemCarbo Arm Only						
Study Days[a]:	Day -28 to -1	Day 1	Day 3 (- 1 day)	Day 8 (± 3 days)	Days 14-21	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 8 (± 3 days)	Day 15 (± 3 days)	(±7 days)	Rescreening[r]	30 days from last dose (± 7 days)	100 days from last dose (± 7 days)	Every 3 months (± 14 days)
Hematology[h]	X	X		X			X	X		X	X			
Serum chemistry[i]	X	X		X			X			X	X			
Additional laboratory assessments[j]	X						X[i]			X	X			
Urinalysis (dipstick)[k]	X	X					X			X	X			
Serology[j]	X										X			
Tumor biopsy/ PD-L1 status[l]	X				X									
PK and immunogenicity assessments		PK and immunogencity assessments are not applicable to patients receiving GemCarbo. If patient crosses over to NKTR-214/nivolumab, immunogenicity assessments are required, but PK is not applicable. Please refer to Table 4 of protocol Amendment 3.0 or later for immunongenicity assessments after crossover.												
[redacted]		[redacted]												

Appendix 5, Table 1: Schedule of Events for Patients Previously Randomized to GemCarbo (Excluding Pharmacokinetic, Immunogenicity, [redacted] Sampling) (Contd)

Procedure / Period:	Screening	Treatment								Post-treatment				
		Cycle 1 Only					Cycle 2 and Beyond			EOT[q]	Cross Over	Follow-up[s]		Survival Follow-up[t]
Study Days[a]:	Day -28 to -1	Day 1	Day 3 (- 1 day)	Day 8 (± 3 days)	Days 14-21	GemCarbo Arm Only: Day 15 (± 3 days)	Day 1 (± 3 days)	GemCarbo Arm Only: Day 8 (± 3 days)	GemCarbo Arm Only: Day 15 (± 3 days)	(±7 days)	Rescreening[r]	30 days from last dose (± 7 days)	100 days from last dose (± 7 days)	Every 3 months (± 14 days)
Tumor assessment[m]	X	Every 9 weeks (± 7 days) for the first 12 months and every 12 weeks (± 7 days)									X	X	X	
Brain Imaging[n]	X	• Patients with a history of brain metastasis or symptoms should have surveillance MRI with and without contrast per standard of care. • First assessment at 9 weeks (± 7 days) from enrollment, and then approximately every 12 weeks (± 7 days), or sooner if clinically indicated.								• For patients without BICR-confirmed progression, continue to have surveillance MRI with and without contrast per standard of care every 12 weeks (± 7 days), or sooner if clinically indicated.				
Gemcitabine administration		X		X			X	X						
Carboplatin administration		X					X							
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review of concomitant medications	X	X	X	X	X	X	X	X	X	X	X			
Health-related quality of life assessments[u]	X	X					X			X	X	X	X	X

Appendix 5, Table 1: Schedule of Events for Patients Previously Randomized to GemCarbo (Excluding Pharmacokinetic, Immunogenicity, [redacted] Sampling) (Contd)

Procedure / Period:	Screening	Treatment								Post-treatment				
		Cycle 1 Only					Cycle 2 and Beyond			EOT[q]	Cross Over	Follow-up[s]		Survival Follow-up[t]
						GemCarbo Arm Only)		GemCarbo Arm Only						
Study Days[a]:	Day -28 to -1	Day 1	Day 3 (- 1 day)	Day 8 (± 3 days)	Days 14-21	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 8 (± 3 days)	Day 15 (± 3 days)	(±7 days)	Rescreening[r]	30 days from last dose (± 7 days)	100 days from last dose (± 7 days)	Every 3 months (± 14 days)
Long-term follow-up[o]												X	X	
Subsequent medications												X	X	
Subsequent anti-cancer therapy[p]												X	X	X
Survival follow-up (by telephone)														X

AE = adverse events; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for the Research and Treatment of Cancer; EOT = end of treatment; FFPE = formalin-fixed paraffin-embedded; IV = intravenous; LVEF =left ventricular ejection fraction; MUGA = multigated acquisition; Nivo = nivolumab; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetic(s); SAE = serious adverse event.

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

b. Physical examination will include a targeted physical examination on Day 1 of each cycle, which must occur within 5 days prior to administering study drugs; see Section 9.8 of protocol Amendment 3.0 or later.

c. Some clinic visits will have more frequent vital sign measurements. Vital sign assessments for Day 1 of each cycle must occur within 5 days prior to administering study drugs. Blood pressure evaluation pre dose Cycle 1 Day 1 and on Cycle 1 Day 3 will include orthostatic blood pressure measurements. Vital signs for GemCarbo should be collected per standard of care. See Sections 6.2.1 and 9.9 of protocol Amendment 3.0 or later.

d. ECOG performance status assessments for Day 1 of each cycle must occur within 5 days prior to administering study drugs.

e. ECG must be done within 14 days of Day 1. See Section 9.10 of protocol Amendment 3.0 or later.

f. A standard echocardiogram or MUGA will be performed for all patients within 60 days prior to dosing Cycle 1 Day 1 to assess for cardiac function and LVEF. See Section 9.11 of protocol Amendment 3.0 or later.

g. See Section 9.5.1 of protocol Amendment 3.0 or later.

h. Screening hematology must be done within 14 days of Day 1. Hematology assessments for Day 1 of each cycle must be drawn within 5 days prior to administering study drugs. See Appendix 2 of protocol Amendment 3.0 or later.

i. Screening serum chemistry must be done within 14 days of Day 1. See Appendix 2 of protocol Amendment 3.0 or later.

j. See Appendix 2 of protocol Amendment 3.0 or later. The sampling for additional tests can be drawn within 5 days prior to administration of study drugs.

k. See Appendix 2 of protocol Amendment 3.0 or later. Urinalysis assessment for Day 1 of each cycle must be provided within 5 days prior to administering study drugs.

l. Unstained FFPE, tumor tissue sections on slides (a minimum of 10 slides, preferably 15 to 25) or a FFPE tumor tissue block, collected within 12 months prior to enrollment and without intervening therapy, are acceptable in lieu of a fresh tumor biopsy prior to treatment. See Appendix 5, Section 4.2 and Section 7.5 of protocol Amendment 3.0 or later. An optional on-treatment tumor tissue sample will be collected prior to Cycle 2 Day 1, on Days 14 to 21 of Cycle 1. Sample collection upon disease progression is optional but highly recommended. PD-L1 status is described in Section 7.3 of protocol Amendment 3.0 or later. If patient crosses over to NKTR-214/nivolumab treatment, a biopsy at rescreening is not required.

m. Tumor assessments at Screening and every 9 weeks (± 7 days) from Cycle 1 Day 1 for the first 12 months. Beyond 12 months, tumor assessments will decrease in frequency to every 12 weeks (± 7 days). A scan should also be done at EOT unless a scan was done within 4 weeks (Section 7.0 of protocol Amendment 3.0 or later). Patients who continue treatment beyond progression should continue to have scans every 9 weeks (± 7 days) for the first 12 months of treatment post-progression and every 12 weeks (± 7 days) in the second year of treatment post-progression. Tumor assessments in the follow-up period are only needed if the patient discontinued treatment without radiographic disease progression (Section 4.1.4 of protocol Amendment 3.0 or later). Confirmation of tumor response is discussed in Section 8.3 of protocol Amendment 3.0 or later. Scans will be sent to imaging vendor.

n. At rescreening, an MRI of the brain without and with contrast is required for patients within 28 days prior to enrollment. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 7.0 of protocol Amendment 3.0 or later for further details.

o. See Section 4.1.4 of protocol Amendment 3.0 or later.

p. Additional subsequent cancer 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 anti-cancer therapies will be collected.

q. See Section 4.1.3 of protocol Amendment 3.0 or later. Patients not crossing over to NKTR-214/nivolumab should continue with the Follow-up Visits 30 days and 100 days after the last dose of study treatment as well as the Survival Follow-Up Visits.

r. Patients crossing over to NKTR-214/nivolumab should proceed with rescreening assessments. See Appendix 5, Section 3.3.

s. Patients must be followed for at least 100 days after the last dose of study treatment. Follow-up Visit 1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose. Follow-up Visit 1 can be combined with the EOT Visit if the visits are within 7 days of each other. Follow-up Visit 2 occurs approximately 100 days (± 7 days) from the last dose of study treatment. Both follow-up visits should be conducted at the clinic. See Section 4.1.4 of protocol Amendment 3.0 or later.

t. All patients will be contacted for post-study therapy(ies) and survival every 3 months (± 14 days) following the Day 100 follow-up visit. The study 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. See Section 4.1.4 of protocol Amendment 3.0 or later.

u. At each visit specified, health-related quality of life (HRQoL) will be assessed using the EORTC Quality of Life Questionnaire (EORTC QLQ-C30); general health status will be measured using the EuroQol Group's EQ-5D questionnaire (EQ-5D-3L) and treatment burden will be captured by the Functional Assessment of Chronic Illness Therapy (FACIT) GP5 item. During long-term survival follow-up, the EQ-5D-3L will be administered by telephone. See Section 7.6 of protocol Amendment 3.0 or later.

2.0 INVESTIGATIONAL PLAN FOR PATIENTS PREVIOUSLY RANDOMIZED TO GEMCITABINE/CARBOPLATIN (GEMCARBO)

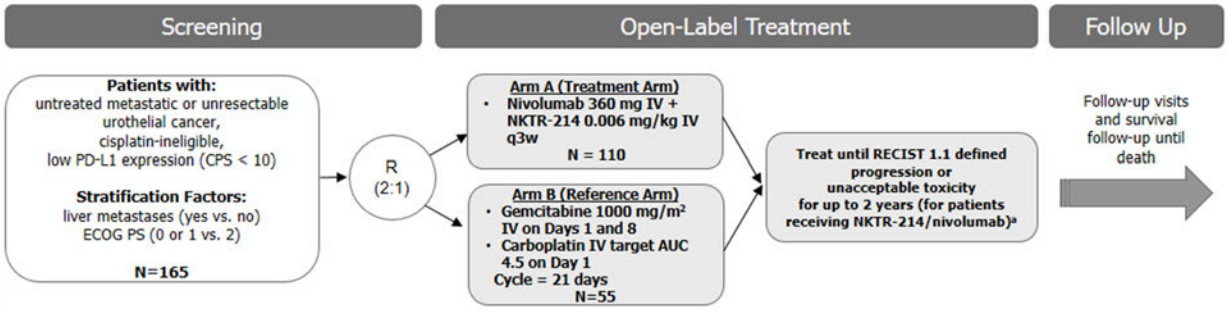
2.1 Background

This appendix describes the treatment plan for patients who were randomized to gemcitabine and carboplatin (GemCarbo) in an earlier version of the protocol. This information is being included for reference purposes, as patients who were randomized to GemCarbo in an earlier version of the protocol should continue receiving GemCarbo as described in Appendix 5, Section 2.3. For information pertaining to study procedures for patients randomized to GemCarbo that is not covered in the appendix, refer to Amendment 2.0 of the protocol.

In an earlier version of the protocol, some patients were randomized to receive: gemcitabine 1000 mg/m^2 intravenous (IV; on Day 1 and 8 of each 3-week cycle) and carboplatin IV, target area under the curve (AUC) 4.5 mg/mL/min q3w (on Day 1 of each 3-week cycle) (Arm B, Reference Arm).

Appendix 5, Figure 1 provides the study schematic for Amendment 2.0. Appendix 5, Table 1 outlines the study procedures in the Schedule of Events.

Appendix 5, Figure 1: Study Schematic for Amendment 2.0



AUC = area under the curve; CPS = Combined Positive Score; PD-L1 = programmed cell death ligand 1; q3w = every 3 weeks; PS = performance status; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1

a. Patients treated with GemCarbo may cross over to treatment with NKTR-214/nivolumab. See Appendix 5, Section 3.3 for additional information.

Please note references to Amendment 3.0 in this Appendix refer to Amendment 3.0 or the current version of the protocol in effect at your site; to reflect this the terminology 'Amendment 3.0 or later' has been utilized in this appendix.

2.2 Screening Period

Patients should have completed the screening period before randomization to GemCarbo.

2.3 Treatment Period

Every effort should be made to schedule visits within the protocol-specified windows (Appendix 5, Table 1).

GemCarbo may be administered for a total of 4 to 6 cycles (or longer) per the treating facilities institutional standard, until unacceptable toxicity, or progressive disease. Patients who have not had progressive disease at the end of their GemCarbo treatment should continue treatment per Investigator recommendations.

Patients treated with GemCarbo may cross over and receive treatment with NKTR-214/nivolumab if they meet any of the following:

- RECIST 1.1 defined progressive disease
- Unacceptable toxicity making completion of 4 to 6 cycles of GemCarbo not feasible
- Residual disease upon completion of 4 to 6 cycles of GemCarbo

See Appendix 5, Section 3.3 for additional information about GemCarbo cross-over.

3.0 GEMCARBO STUDY TREATMENTS

Study treatment for patients receiving GemCarbo are detailed in Appendix 5, Table 2.

Appendix 5, Table 2: GemCarbo Treatment for Study 18-214-10

Product Description / Class and Dosage Form	Potency	IMP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Gemcitabine Powder for Solution for Injection	200 mg or 1 g (10 mg/mL)	IMP	Open-label	Vial (one or more vials per carton)	Store below 30°C; do not refrigerate.
Carboplatin Solution for Injection	5 mL/15 mL/45 mL vials containing 50 mg/150 mg/450 mg (10 mg/mL)	IMP	Open-label	Vial (one or more vials per carton)	Store at room temperature

IMP = Investigational Medicinal Product

3.1 Administration of Study Drugs

3.1.1 Gemcitabine

Gemcitabine 1000 mg/m^2 will be given on Days 1 and 8 of each 21-day cycle and prepared per institutional guidelines and/or package insert. An appropriate amount of drug will be prepared and administered as a continuous infusion over approximately 30 to 60 minutes, with a 30-minute infusion considered ideal. Prolonged infusion time increases the toxicity.

Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1 g of gemcitabine as the hydrochloride salt, mannitol, and sodium acetate. The lyophilized product should be stored below 30°C. Gemcitabine should be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/mL. The concentration for 200 mg and 1 g vials should be no greater than 40 mg/mL. Once the drug has been reconstituted it should be stored at room temperature and used within 24 hours or per institutional guideline.

All patients should receive pre-medications (see Appendix 5, Section 3.1.4).

3.1.2 Carboplatin

The total dose of carboplatin is based on renal function and calculated by the Calvert formula (Calvert, 1989) using the target AUC (4.5 mg/mL/min) and glomerular filtration rate (GFR):

$$\text{Total dose in mg} = 4.5 \times (\text{GFR} + 25)$$

GFR will be assessed by direct measurement (ethylene diamine tetraacetic acid [EDTA] clearance or creatinine clearance) or, if not available, by calculation from serum/plasma creatinine (Cockcroft and Gault formula). Per institutional standard, GFR may be capped at 125 mL/minute.

Carboplatin is to be given on Day 1 of each treatment cycle and prepared per institutional guidelines and/or package insert. An appropriate amount of drug will be prepared and administered IV as a continuous infusion per institutional guidelines.

Carboplatin is supplied in 5 mL, 15 mL, or 45 mL vials containing 50 mg, 150 mg, or 450 mg carboplatin and water for injection.

All patients should receive pre-medications (see Appendix 5, Section 3.1.4).

3.1.3 Vital Sign Monitoring

Vital signs of patients receiving GemCarbo should be collected at a minimum on Day 1 of all cycles. Additional vital signs may be collected per standard practice of the site.

3.1.4 Premedication for Patients Receiving GemCarbo

All patients must receive prophylaxis for acute and delayed emesis. One of the following regimens is suggested, however sites may use other regimens per their standard practice:

a) Ondansetron 16 to 24 mg and dexamethasone 12 mg orally (PO) ± aprepitant 125 mg PO 30 minutes before Day 1 of GemCarbo.

b) Granisetron 1 mg to 2 mg and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before Day 1 of GemCarbo.

c) Dolasetron 100 mg and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before Day 1 of GemCarbo.

d) Palonosetron 0.25 mg IV and dexamethasone 12 mg PO ± aprepitant 125 mg PO 30 minutes before Day 1 of GemCarbo.

3.2 Dosage Modification

3.2.1 Gemcitabine/Carboplatin Dose Modification Criteria

Dose modifications for gemcitabine or carboplatin or both may be made for hematological, renal, or other toxicities. Investigators should follow the approved prescribing guidelines in the country, or institutional standard of care. Recommended dose modifications are below, however institutions may follow institutional standard of care if variances are noted.

3.2.1.1 Hematological Toxicity

A complete white blood cell (WBC) count, absolute neutrophil count (ANC), and platelet count is to be on Days 1 and 8 of each treatment cycle. Additional labs should be performed per standard of care. Dose modifications are shown in Appendix 5, Table 3.

Appendix 5, Table 3: Dose Modification and Delay for Gemcitabine and Carboplatin Due to Hematological Toxicity (Cycle 1)

Criterion					Modification	
WBC ($\times 10^9$/L)	And/Or	ANC ($\times 10^9$/L)	And/Or	Platelets ($\times 10^9$/L)	% Dose of Gemcitabine	% Dose of Carboplatin
Day 1:						
≥ 3.0	and	≥ 1.5	and	≥ 100	100	100
< 3.0	or	< 1.5	or	< 100	Delay 1 week	Delay 1 week
Day 8:						
≥ 3.0	and	> 1.5	and	≥ 100	100	NA
≥ 2.0 – 3.0	and	≥ 1.0	and	>100	100	NA
1.0 – 1.9	or	> 0.5 - <1.0	or	50-99	50	NA
< 1.0	or	< 0.5	or	< 50	Withhold	NA

ANC = absolute neutrophil count; NA = not applicable; WBC = white blood cells

Dose modifications for subsequent cycles are as follows:

- At Day 1, 25% dose reduction of each drug if during the nadir one or more of the following occurs:
- Grade 4 neutropenia (ANC < 0.5×10^9/L) with fever > 38.5 °C or
- Grade 4 thrombocytopenia (< 10.0×10^9/L) for more than 3 days or
- Thrombocytopenia with active bleeding during the nadir.

If a patient requires more than 2 weeks for hematologic recovery (defined as, at minimum, WBC is ≥ 2.0×10^9/L, ANC ≥ 1.0×10^9/L and platelets ≥ 75×10^9/L), treatment should be continued with 75% of dose of each drug.

3.2.1.2 Renal Toxicity

Carboplatin will be adjusted every cycle using Calvert's formula.

For gemcitabine, no dose modification is necessary if the GFR is ≥ 30 mL/min. Gemcitabine is withheld if the GFR is < 30 mL/min.

3.2.1.3 Other Toxicities

Dose reductions for gemcitabine and carboplatin for drug-related toxicities are made as follows:

- Grade 1-2: no dose reductions.
- Grade 3: 25% dose reduction in both drugs

- Grade 4: the patient may be withdrawn from the study at the Investigators discretion. If the patient continues under treatment, a 50% dose reduction should be considered.

In case of nausea and vomiting, adequate parenteral fluid, electrolyte substitution and application of modern antiemetics and dexamethasone, if necessary should be done. The diagnosis of hemolytic uremic syndrome (HUS) should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or lactate dehydrogenase (LDH), reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or blood urea nitrogen [BUN]). Gemcitabine therapy should be discontinued immediately upon diagnosis of HUS.

3.3 GemCarbo Cross Over to NKTR-214/Nivolumab

Patients treated with GemCarbo may cross over and receive treatment with NKTR-214/nivolumab if they meet any of the following:

- RECIST 1.1 defined progressive disease
- Unacceptable toxicity making completion of 4 to 6 cycles of GemCarbo not feasible
- Residual disease upon completion of 4 to 6 cycles of GemCarbo

The decision to cross over should be made by the patient in collaboration with their treating physician. Patients are required to complete the GemCarbo end of treatment (EOT) visit. Patients need to provide consent to cross over to NKTR-214 and nivolumab treatment and must complete the required rescreening evaluations within 28 days of beginning NKTR-214 and nivolumab treatment.

Upon initiation of treatment with NKTR-214/nivolumab patients should follow the assessment schedule outlined in the schedule of assessments (Table 1) of Amendment 3.0 or later for patients undergoing treatment with NKTR-214/nivolumab (starting with Cycle 1 Day 1). The Cycle 1 Day 1 visit should occur no more than 90 days after the GemCarbo EOT visit. No intervening treatment between GemCarbo and NKTR-214/nivolumab is allowed. Patients will need to have immunogenicity blood samples done as per Table 4 of protocol Amendment 3.0 or later. Patients do not need to undergo the PK or biomarker draws listed in Table 4 of protocol Amendment 3.0 or later. Patients also do not need to undergo the biopsies outlined in Table 6 of protocol Amendment 3.0 or later.

To be eligible for cross over, patients must meet all eligibility criteria as defined in Sections 5.1 and 5.2 of protocol Amendment 3.0 or later.

4.0 STUDY ASSESSMENTS AND PROCEDURES

4.1 Pharmacokinetic, Immunogenicity [redacted] Measurements for GemCarbo

PK and immunogencity assessments are not applicable to patients receiving GemCarbo. If patient crosses over to NKTR-214/nivolumab, immunogenicity assessments are required, but PK is not applicable. Please refer to Table 4 of of protocol Amendment 3.0 or later for immunongenicity assessments after crossover. See Appendix 5, Section 3.3.

[redacted]

4.2 Tumor Tissue Specimens

An optional on-treatment tumor tissue sample will be collected prior to Cycle 2 Day 1, on Days 14 to 21 of Cycle 1 and at the time of disease progression (Appendix 5, Table 5). See Section 7.5 of protocol Amendment 3.0 or later for additional information regarding tumor tissue sample collection.

Appendix 5, Table 5: Tumor Biopsy Sampling Schedule

Collection Timing	Tumor Biopsy
Screening	X[a]
Cycle 1 Days 14-21[b]	X
Upon progression[b]	X

a. Unstained FFPE, tumor tissue sections on slides (minimum of 10, preferably 15 to 25) or a FFPE tumor tissue block, collected within 12 months prior to enrollment and without intervening therapy, are acceptable in lieu of a fresh tumor biopsy prior to treatment.

b. Sample collection is optional but highly recommended.

5.0 ASSESSMENT OF SAFETY

5.1 Adverse Event and Serious Adverse Event Follow-Up

For patients receiving GemCarbo, after initiation of study drug treatment, all AEs will be reported starting immediately after the patient has been administered the first dose of study drug(s) until 30 days after the last dose of study drug(s).

For patients receiving GemCarbo, all SAEs, regardless of causality, with an onset within 100 days after the last dose of study drug(s) will be reported to Nektar Therapeutics Drug Safety immediately without undue delay, under no circumstances later than 24 hours following knowledge.

Additional information pertaining to AEs and SAEs is provided in Sections 9.1 to 9.4 of protocol Amendment 3.0 or later.

5.2 Pregnancy Tests/Pregnancy

5.2.1 Pregnancy Tests

Serum or urine pregnancy tests will be performed on WOCBP during screening. Serum or urine pregnancy tests will be performed on women on 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 3 of protocol Amendment 3.0 or later) 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 9.5.2 of protocol Amendment 3.0 or later.

5.2.2 Pregnancy

5.2.2.1 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 6 months after the last dose of study treatment for female patients receiving GemCarbo. Women who become pregnant during and for up to 6 months after treatment with carboplatin should be offered genetic consultation by their treating institution. 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 9.2.2 of protocol Amendment 3.0 or later. 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.

5.2.2.2 Pregnancies in Female Partners of Male Patients

Any pregnancy occurring during the course of the study and for 6 months after the last dose of GemCarbo 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. 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 9.2.2 of protocol Amendment 3.0 or later. 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.

5.3 Other Safety Assessments

Additional information pertaining to the assessment of safety is provided in Sections 9.6 to 9.11 of protocol Amendment 3.0 or later.

6.0 REFERENCES

Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol. 1989;7:1748–1756.

APPENDIX 6: CYTOKINE RELEASE SYNDROME (CRS) MANAGEMENT ALGORITHM

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

CRS Management Measures/Algorithm

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

For patients with suspected CRS:

- For Grade 1 or Grade 2 events, implement supportive care, including management of isolated symptoms based on institutional practices.
- Consider admitting the patient for monitoring and providing supportive care, including management of isolated symptoms based on institutional practices and protocol management guidelines (e.g., hydration management guidelines, Section 6.2.2).
- 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 eight hours, dexamethasone 10 mg up to four times daily, 1-2 mg/kg/day methylprednisolone IV or PO equivalent) - High dose steroid (e.g., methylprednisolone 2 mg/kg up to 1 gram daily for three 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	