Protocol 19-255-03

A PHASE 1B/2, OPEN-LABEL, MULTICENTER, DOSE ESCALATION AND DOSE EXPANSION STUDY OF NKTR-255 MONOTHERAPY OR IN COMBINATION WITH CETUXIMAB AS A SALVAGE REGIMEN FOR SOLID TUMORS

NCT04616196

Approval Date: 08 October 2021

Nektar Therapeutics

CLINICAL STUDY PROTOCOL

A PHASE 1B/2, OPEN-LABEL, MULTICENTER, DOSE ESCALATION, AND DOSE EXPANSION STUDY OF NKTR-255 MONOTHERAPY OR IN COMBINATION WITH CETUXIMAB AS A SALVAGE REGIMEN FOR SOLID TUMORS

Protocol Number:	19-255-03
Protocol Date:	08 October 2021
Protocol Amendment Number:	2.0
Supersedes:	Amendment 1.0 dated 07 August 2020 Original Protocol dated 19 June 2020
US IND Number:	146,184
Ex US:	Non-IND
Eudra CT No.:	2021-002177-25
Investigational Products:	NKTR-255 and NKTR-255 in combination with cetuximab
Indication:	Relapsed or refractory advanced solid tumors
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA PPD
Sponsor's Medical Contact and Study Medical Monitor:	PPD

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

TITLE:	**A PHASE 1B/2, OPEN-LABEL, MULTICENTER, DOSE ESCALATION, AND DOSE EXPANSION STUDY OF NKTR-255 MONOTHERAPY OR IN COMBINATION WITH CETUXIMAB AS A SALVAGE REGIMEN FOR SOLID TUMORS**
PROTOCOL NUMBER:	19-255-03
PHASE OF STUDY:	1B/2
PROTOCOL DATE:	08 October 2021
PROTOCOL AMENDMENT NO:	2.0
SUPERSEDES:	Amendment 1.0 dated 07 August 2020
STUDY SPONSOR:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

PRINCIPAL INVESTIGATOR COMMITMENT:

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

_____

Principal Investigator Printed Name

_____ _____

Principal Investigator Signature **Date**

Institution:

Address:

PROTOCOL APPROVAL PAGE

A PHASE 1B/2, OPEN-LABEL, MULTICENTER, DOSE ESCALATION, AND DOSE EXPANSION STUDY OF NKTR-255 MONOTHERAPY OR IN COMBINATION WITH CETUXIMAB AS A SALVAGE REGIMEN FOR SOLID TUMORS

PROTOCOL NUMBER: 19-255-03

PHASE: 1B/2

PROTOCOL DATE: 08 October 2021

PROTOCOL AMENDMENT NO: 2.0

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

PPD

Printed Name:
Position:

LIST OF STUDY CONTACTS

PPD

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ABBREVIATIONS

Abbreviation or Term	Definition
5-FU	5-fluorouracil
CCI	[redacted]
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	absolute neutrophil count
anti-HBc	antibodies to hepatitis B core antigens
anti-HBs	antibodies to hepatitis B surface antigens
anti-PD-1	antibody to programmed cell death protein 1
anti-PD-L1	antibody to programmed death-ligand 1
anti-PD-(L)1	anti-PD-1 antibody or anti-PD-L1 antibody
ASBMT	American Society for Blood and Marrow Transplantation
CCI	[redacted]
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the concentration-time curve
β	beta
β-HCG	beta subunit of human chorionic gonadotropin
BiPAP	bilevel positive airway pressure
BLRM	Bayesian logistic regression model
BOR	best overall response
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BUN	blood urea nitrogen
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum peak concentration
CnDn	Cycle n Day n (eg, Cycle 1 Day 1 = C1D1)
CO_2	carbon dioxide
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CR	complete response

Abbreviation or Term	Definition
CRC	colorectal carcinoma or colorectal cancer
CRS	cytokine release syndrome
CCI	[redacted]
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DCI	data collection instrument
DLT	dose-limiting toxicity
dMMR	mismatch repair deficient
DOR	duration of response
DSMC	Data Safety Monitoring Committee
EBV	Epstein-Barr virus
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOI	end of infusion
EOT	end of treatment
eSAE	electronic serious adverse event
ESS	effective sample size
EWOC	escalation with overdose control
FDA	Food and Drug Administration
FIH	first-in-human
γ	gamma
GCP	Good Clinical Practice (guidelines)
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice (guidelines)
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCT	hematocrit
HCV	hepatitis C virus
HCV-RNA	hepatitis C virus ribonucleic acid
Hep B	hepatitis B
Hep C	hepatitis C
HER2	human epidermal growth factor receptor 2

Abbreviation or Term	Definition
Hgb	hemoglobin
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
hr	hour
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IFNα	interferon alpha
IgG1	immunoglobulin gamma-1
IHC	immunohistochemistry
IL-2	interleukin-2
IL-15	interleukin-15
IL-15Rα	IL-15 receptor alpha
IL-n	interleukin-n (eg, interleukin 2 = IL-2)
IND	Investigational New Drug (application)
IRB	institutional review board
IRR	infusion-related reaction
CCI	[redacted]
IV	intravenous(ly)
JAK-STAT5	Janus kinase/signal transducer and activator of transcription-5
kDa	kilodalton
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov chain Monte Carlo
MCP-1	monocyte chemoattractant protein-1
mCRC	metastatic colorectal carcinoma
MCV	mean corpuscular volume
MM	multiple myeloma
mmHg	millimeters of mercury
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI	microsatellite instability

Abbreviation or Term	Definition
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer
NKT	natural killer T cells
NRAS	neuroblastoma RAS viral oncogene homolog
ORR	objective response rate
OS	overall survival
PaO_2	oxygen saturation
PD	pharmacodynamic(s)
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PEG	polyethylene glycol
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
q21d	every 21 days
q28d	every 28 days
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-15	recombinant human interleukin-15
RP2D	recommended Phase 2 dose
R/R	relapsed or refractory
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCC	squamous cell carcinoma
sCD25	soluble CD25
SD	stable disease
sIL-15Rα	soluble IL-15 receptor alpha
SOI	start of infusion
SOP	standard operating procedure
SRC	Safety Review Committee

Abbreviation or Term	Definition
STAT5	signal transducer and activator of transcription-5
sTNF RI	soluble tumor necrosis factor receptor I
sTNF RII	soluble tumor necrosis factor receptor II
$t_{1/2}$	half-life
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TNF	tumor necrosis factor
TP	total protein
TSH	thyroid-stimulating hormone
TTR	time to response
UDP	uridine diphosphate
ULN	upper limit of normal
US	United States
USA	United States of America
V	volume of distribution
WBC	white blood cell
WCBP	women of childbearing potential

1.0 STUDY SYNOPSIS

Name of Sponsor:	Nektar Therapeutics
Name of Finished Products:	NKTR-255 Drug Product Erbitux®
Name of Active Ingredients:	NKTR-255 Drug Substance Cetuximab
Title of Study:	A Phase 1b/2, Open-label, Multicenter, Dose Escalation, and Dose Expansion Study of NKTR-255 Monotherapy or in Combination with Cetuximab as a Salvage Regimen for Solid Tumors
Duration of Treatment:	In Phase 1b, patients will receive an intravenous (IV) loading dose of cetuximab alone, followed 7 days later by the first combination treatment of IV cetuximab and IV NKTR-255 on Cycle 1 Day 1 (C1D1). Thereafter, IV NKTR-255 will be given in 21-day cycles in combination with weekly IV cetuximab. In Phase 2, patients will receive either NKTR-255 in combination with cetuximab in 21-day cycles or will receive NKTR-255 monotherapy in 21-day cycles. Patients who achieve optimal response in the NKTR-255 in combination with cetuximab cohorts may move to NKTR-255 monotherapy maintenance given in 28-day cycles. Patients will remain on treatment until meeting one of the criteria for discontinuation of treatment in Section 5.2.3.1.
Phase of Development:	Phase 1b/2
Objectives:	The primary objectives are: Phase 1b (Dose Escalation): • To evaluate the safety and tolerability, as well as define the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D), of NKTR-255 in combination with cetuximab in relapsed or refractory (R/R) head and neck squamous cell carcinoma (HNSCC) or colorectal carcinoma (CRC) Phase 2 (Dose Expansion): • To evaluate the safety and tolerability of NKTR-255 monotherapy and NKTR-255 in combination with cetuximab in R/R HNSCC, CRC, CCI [redacted] • To evaluate the efficacy of NKTR-255 in combination with cetuximab in R/R HNSCC or CRC by assessing the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 The secondary objectives are: • To evaluate the efficacy of NKTR-255 monotherapy in R/R CCI [redacted] by assessing the ORR by RECIST 1.1 • To evaluate the efficacy of NKTR-255 in combination with cetuximab and NKTR-255 monotherapy by assessing progression-free survival (PFS) and overall survival (OS) [redacted] CCI [redacted]

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Study Population:	Adults at least 18 years of age having R/R cancer of one of the following tumor types: • HNSCC • CRC CCI
Number of Patients (planned):	Phase 1b Dose Escalation: Approximately 30 patients Phase 2 Dose Expansion: CCI
Number of Study Sites:	CCI
Countries:	United States (US) and rest of world
Study Design:	This study is a Phase 1b/2, open-label, multicenter, dose escalation, and dose expansion study in patients with R/R HNSCC, CRC CCI **Phase 1b – Dose Escalation** • The NKTR-255 starting dose will be 1.5 µg/kg IV, which had no safety concerns as defined by pre-specified dose-limiting toxicities in the first cohort of the ongoing first-in-human (FIH) study Protocol 18-255-02. The starting dose is based on ongoing safety data generated from the escalation cohorts and the RP2D determination from the FIH study. The starting dose will not be greater than the highest dose determined by the Safety Review Committee (SRC) to have no safety concerns in the FIH study. • After an initial cetuximab loading dose of 400 mg/m^2 IV during the study run-in period (Day -7), patients will receive IV NKTR-255 every 21 days (q21d) in combination with 250 mg/m^2 IV cetuximab weekly. On days that NKTR-255 and cetuximab are both dosed, cetuximab should be administered first, followed by NKTR-255 a minimum of 1 hour later but within 3 hours of completing the cetuximab infusion. Beginning with Dose Level 1, successive dose levels of at least 3 patients will receive ascending doses of NKTR-255 until the MTD and/or RP2D is determined. Approximately 30 patients will be enrolled in the dose escalation phase of the study. A 2-parameter Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle (Neuenschwander, 2008) will be used as a guide during the escalation phase of the study for dose level selection and for determination of the MTD and/or RP2D. Additional groups may also be opened to further explore the MTD. For details, refer to Sections 5.1, 5.8, and 5.9.

The first patient (a sentinel patient) of each escalating NKTR-255 dose level will be monitored for safety and tolerability for 7 days after the first dose of NKTR-255 before additional patients are dosed at the same dose level.

A composite of clinical information will be used to select the RP2D based on safety and tolerability, PK, PD, and optimal biological response. Additional patients may be enrolled to refine the RP2D, and a minimum of 6 patients will be required to define the RP2D.

The dose-limiting toxicity (DLT) window is 21 days after the first dose of NKTR-255. Patients who achieve optimal response (partial response [PR] or complete response [CR] per RECIST 1.1) after at least 1 tumor assessment, as determined by the Investigator and in consultation with the Medical Monitor, will be given the option to continue treatment with NKTR-255 as single agent for maintenance every 28 days (q28d) at the same dose as the patient's originally assigned dose.

- Intermediate doses may be evaluated.
- No intra-patient dose escalation will be allowed.
- Enrollment into a new dose level with an escalating dose of NKTR-255 cannot begin until the DLT window has closed for at least 3 patients in the prior dose level.
- The SRC will assess safety before opening dose escalation to the next level.
- The Sponsor's decision to declare the RP2D of NKTR-255 can occur at any given dose level prior to reaching the MTD based on safety, PK, CCI effects.
- Data from a minimum of 6 evaluable patients are required to define the RP2D.
- Dose reduction of NKTR-255 is not allowed during dose escalation within the DLT window. Outside of the DLT window in the dose escalation phase, and during dose expansion, dose levels of NKTR-255 may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested (the dose level may be de-escalated in order to characterize RP2D for a specific dose level).
- The cetuximab dose may be reduced or adjusted based on review of available safety and tolerability data. Dose adjustment or discontinuation for cetuximab may be required

	based on emerging toxicities, and should follow the guidelines specified in this protocol and in the current local prescribing information for cetuximab. [redacted]
Key Eligibility Criteria:	Each patient must meet all of the following criteria to be enrolled in the study (for both dose escalation and dose expansion phases): • Histologically confirmed diagnosis of a locally-advanced (not amenable to curative therapy such as surgical resection or radiotherapy) or metastatic cancer of the following histologies: HNSCC, CRC, [redacted] • Life expectancy > 12 weeks as determined by the Investigator. • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. • Measurable disease per RECIST 1.1.

- Patients who have received systemic interferon alpha (IFNα) within the previous 6 months prior to enrollment in the study are not eligible.
- Patients who have been previously treated with interleukin-2 (IL-2) or IL-15 are not eligible.
- Demonstrated adequate organ function within 14 days before C1D1.
- Patients with other active malignancy are not eligible, with the exception of: basal cell carcinoma of the skin, SCC of the skin that has undergone potentially curative therapy, in situ cervical cancer, or prostate cancer under certain circumstances. Patients with simultaneous diagnosis of cSCC and hematologic malignancy (eg, chronic lymphocytic leukemia [CLL]) are allowed.
- Patients who have previously received cetuximab or other epidermal growth factor receptor (EGFR)-directed therapies are excluded from Phase 2 of the trial, unless cetuximab was given as part of a primary treatment approach, with no progressive disease for at least 4 months following the end of prior cetuximab treatment.

Head and Neck Squamous Cell Carcinoma

- Patients must have histologically or cytologically confirmed advanced, recurrent, or metastatic HNSCC that could not be treated with curative intent. “Advanced” is defined as either locally advanced HNSCC not amenable to curative surgery or radiotherapy or with distant metastases.
- Patients who have undergone treatment with antibody to programmed cell death protein 1 (anti-PD-1) or antibody to programmed death-ligand 1 (anti-PD-L1) (together termed "anti-PD-(L)1") must have had the last dose of antibody at least 4 weeks prior to receiving any study drug and evidence of tumor progression before they can be enrolled into this study.
- Patients must have known status by pathology for human papillomavirus (HPV) and Epstein-Barr virus (EBV) in HNSCC, either metastatic or recurrent disease.
- Patients must have experienced progression (or toxicity precluding additional treatment) on any first- or second-line platinum-based chemotherapy and anti-PD-(L)1 antibody, unless they are ineligible for such treatment, **OR**,
- Patients must be ineligible for platinum-based (either cisplatin or carboplatin) chemotherapy or chemoradiation due to decline in renal function and/or patient's intolerance.

Colorectal Cancer

- Patients must have a histologically or cytologically confirmed diagnosis of advanced CRC; patients in Phase 2 must have confirmed *KRAS* (US) or *RAS* (ex-US) wild type EGFR-expressing advanced CRC. “Advanced” is defined as either locally advanced unresectable cancer or metastatic disease.
- Patients must have received at least 2 prior cancer therapy regimens administered for metastatic disease including fluoropyrimidine, irinotecan, and oxaliplatin, unless ineligible or intolerant for such treatment.
- Patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors must have been exposed to checkpoint inhibitors such as anti-PD-1.

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Test Product, Dose and Mode of Administration:	CCI NKTR-255 will be given q21d as monotherapy and in combination with cetuximab, and q28d as single-agent maintenance for patients previously treated with NKTR-255 in combination with cetuximab. Administration of cetuximab will be according to the current local prescribing information. Cetuximab will be administered IV weekly (at a dose of 400 mg/m^2 IV as an initial loading dose alone, then at a dose of 250 mg/m^2 IV in combination with NKTR-255).
Safety:	Assessment of safety will occur by ongoing review of the following: • incidence of adverse events (AEs), including serious AEs (SAEs) • clinical laboratory tests (blood and urine sampling) • vital signs • electrocardiograms (ECG) and cardiac function tests • physical examination
Pharmacokinetics:	Blood samples for NKTR-255 and/or cetuximab PK analyses will be collected from patients (respective to treatment) at multiple scheduled sampling times. Plasma concentrations of NKTR-255 and cetuximab will be determined using validated methods. Pharmacokinetic parameters such as maximum peak concentration (C_{max}), area under the concentration-time curve (AUC), clearance (CL), volume of distribution (V), and half-life ($t_{1/2}$) will be estimated from plasma concentration-time data where possible.

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Efficacy:	Tumor measurements will be performed every 9 weeks + 7 days. The primary efficacy measurement will be ORR by RECIST 1.1. CCI
Statistical Methods:	**Safety:** Safety assessments will include AEs, including incidence of SAEs, clinical laboratory tests, vital signs, physical examinations, cardiac function tests, and ECGs. The incidence of DLTs will be evaluated for each dose level. All treatment-emergent adverse events (TEAEs) will be summarized by system organ class and preferred term for each dose level or cohort in the dose escalation and dose expansion phases of the study separately. All TEAEs will be summarized by incidence, severity, and relationship to study drug(s). Clinical laboratory tests and vital signs will be summarized descriptively for each dose level in the dose escalation phase and separately for the dose expansion phase of the study. All abnormal findings in clinical laboratory test results, vital signs, physical examination, cardiac function tests, and ECGs will be listed. **Efficacy:** Objective response rate, CBR, and each BOR category will be calculated along with the 95% confidence intervals (CIs) based on the exact method. The Kaplan-Meier method will be used for the analyses of PFS, OS, and DOR. Time to response will be summarized among responders.

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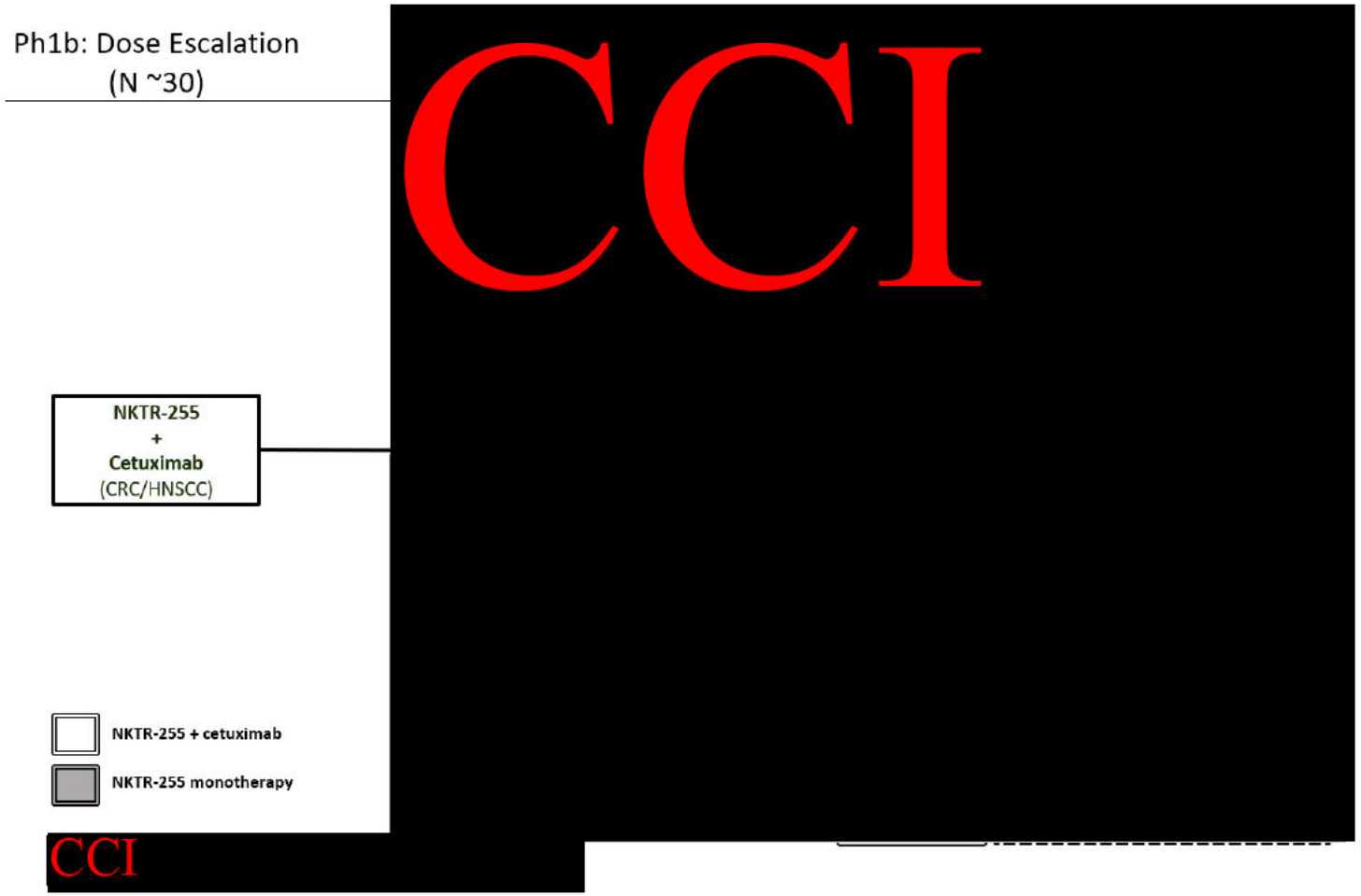
1.1 Study Schematic

Figure 1: Study Schema



CCI CRC = colorectal cancer; CCI HNSCC = head and neck squamous cell carcinoma; Ph = Phase; RP2D = recommended Phase 2 dose

Note: No intra-patient dose escalation will be conducted in any dose level.

Note: The dose-limiting toxicity (DLT) window for NKTR-255 in combination with cetuximab is 21 days following the initial dose of NKTR-255.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1.2 Schedules of Events

Table 1: Schedule of Visits and Assessments – Phase 1b (CRC and HNSCC; NKTR-255 Dose Escalation)

	Screening Period	Treatment Period																								Post-treatment Period		
		Run-in (1 week) Day			Cycle 1 (21-day cycle) Day								Cycle 2 (21-day cycle) Day							Cycle 3 (21-day cycle) Day				Cycle 4+ (21-day cycles) Day					
Event[a]	**≤ 28d prior to Day 1 of Run-in Period**	**-7**	**-6**	**-4**	**1**	**2**	**3**	**4**	**5**	**8**	**10**	**15**	**1**	**2**	**3**	**4**	**8**	**10**	**15**	**1**	**4**	**8**	**15**	**1**	**8**	**15**	**EOT[b]**	**60-day Follow-up[c]**	**Survival Follow-up[c]**
Windows (days)		**+1**			**+1**								**+1**							**+1**				**+1**			**+7**	**±14**	**Every 3 months ±14 days**
Screening Assessments																													
Informed consent	X																												
Inclusion/exclusion criteria	X																												
Demographics	X																												
Medical/cancer history	X																												
Medication/cancer therapy history[d]	X																												
HBV, HCV, HIV serology[e]	X																												
MRI[f]	X																												
General and Safety Assessments																													
Physical examination[g]	X	X			X								X							X				X			X	X	
Weight (kg)[h]	X	X			X								X							X				X			X		
Vital signs[i]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X			X	X	

Table 1: Schedule of Visits and Assessments – Phase 1b (CRC and HNSCC; NKTR-255 Dose Escalation) (Contd)

	Screening Period	Treatment Period																								Post-treatment Period		
		Run-in (1 week) Day			Cycle 1 (21-day cycle) Day								Cycle 2 (21-day cycle) Day							Cycle 3 (21-day cycle) Day				Cycle 4+ (21-day cycles) Day					
Event[a]	**≤ 28d prior to Day 1 of Run-in Period**	**-7**	**-6**	**-4**	**1**	**2**	**3**	**4**	**5**	**8**	**10**	**15**	**1**	**2**	**3**	**4**	**8**	**10**	**15**	**1**	**4**	**8**	**15**	**1**	**8**	**15**	**EOT**[b]	**60-day Follow-up**[c]	**Survival Follow-up**[c]
Windows (days)		**+1**			**+1**								**+1**							**+1**				**+1**			**+7**	**±14**	**Every 3 months ±14 days**
General and Safety Assessments																													
ECOG performance status	X	X			X								X							X				X			X		
Echocardiogram or MUGA or nuclear scan[j]	X																										X		
ECG[k]	X	X			X								X							X							X		
Adverse events review	Continuous from time of ICF until 60 days after last study treatment dose (refer to Sections 7.5 and 7.7)																												
Laboratory Assessments																													
Pregnancy test[l]	X	X			X								X							X				X			X	X	
Hematology[m]	X	X	X	X	X	X		X		X		X	X	X		X	X		X	X		X	X	X			X	X	
Serum chemistry[m]	X	X		X	X			X		X		X	X			X	X		X	X		X	X	X			X	X	
PT/PTT	X	X			X								X							X				X			X	X	
TSH, T4, lipase, amylase, CK[n]	X	X			X								X							X				X			X	X	
Urinalysis	X	X			X								X							X				X			X	X	

Table 1: Schedule of Visits and Assessments – Phase 1b (CRC and HNSCC; NKTR-255 Dose Escalation) (Contd)

Event[a]	Screening Period	Treatment Period																									Post-treatment Period		
		Run-in (1 week) Day			Cycle 1 (21-day cycle) Day								Cycle 2 (21-day cycle) Day							Cycle 3 (21-day cycle) Day				Cycle 4+ (21-day cycles) Day					
	≤ 28d prior to Day 1 of Run-in Period	-7	-6	-4	1	2	3	4	5	8	10	15	1	2	3	4	8	10	15	1	4	8	15	1	8	15	EOT[b]	60-day Follow-up[c]	Survival Follow-up[c]
Windows (days)		+1			+1								+1							+1				+1			+7	±14	Every 3 months ±14 days
PK CCI Assessments																													
PK (NKTR-255)[o] (See Table 7 for sampling times)					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK (cetuximab)[o] (See Table 7 for sampling times)		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

CCI

Table 1: Schedule of Visits and Assessments – Phase 1b (CRC and HNSCC; NKTR-255 Dose Escalation) (Contd)

	Screening Period	Treatment Period																								Post-treatment Period		
		Run-in (1 week) Day			Cycle 1 (21-day cycle) Day								Cycle 2 (21-day cycle) Day							Cycle 3 (21-day cycle) Day				Cycle 4+ (21-day cycles) Day					
Event[a]	**≤ 28d prior to Day 1 of Run-in Period**	**-7**	**-6**	**-4**	**1**	**2**	**3**	**4**	**5**	**8**	**10**	**15**	**1**	**2**	**3**	**4**	**8**	**10**	**15**	**1**	**4**	**8**	**15**	**1**	**8**	**15**	**EOT**[b]	**60-day Follow-up**[c]	**Survival Follow-up**[c]
Windows (days)		**+1**			**+1**								**+1**							**+1**				**+1**			**+7**	**±14**	**Every 3 months ±14 days**
Study Drug Administration																													
NKTR-255 administration[u]					X								X							X				X					
Cetuximab administration[v]		X			X					X		X	X				X		X	X		X	X	X	X	X		
Concomitant medications review	Continuous from time of ICF until 60 days after last study treatment dose																												
Efficacy Assessments																													
Tumor measurements and RECIST 1.1 and irRECIST response assessments[w]	Tumor assessments at Screening and every 9 weeks from C1D1 + 7 days until patients meet one of the criteria for discontinuation of treatment in Section 5.2.3.1.																												
Subsequent therapy/ survival/secondary malignancy information																											X	X	X

AE = adverse event; β-HCG = beta subunit of human chorionic gonadotropin; CK = creatine kinase; CnDn = Cycle n Day n; CRC = colorectal cancer; d = day; ECG = electrocardiogram; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = end of treatment; HBV= hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HNSCC = head and neck squamous cell carcinoma; HPV = human papillomavirus; ICF = informed consent form; irRECIST = immune-related RECIST 1.1; IV = intravenous(ly); LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PaO_2 = oxygen saturation; CCI [redacted] PK = pharmacokinetic(s); PT = prothrombin time; PTT = partial thromboplastin time; q21d = every 21 days; q3 = every 3; RECIST = Response Evaluation Criteria In Solid Tumors; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WCBP = women of childbearing potential

a. All procedures and examinations should be performed before the administration of study drug(s) on dosing days, except as indicated. The acceptable visit window is + 1 day for Day 1. If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. All out-of-window visits and procedures will incur a protocol deviation.

b. The EOT visit should occur within 7 days after study treatment is discontinued, or before a new antineoplastic regimen has been initiated.

c. Safety follow-up visit to occur 60 days after the last dose of study treatment. Survival follow-up visits will occur every 3 months from EOT.

d. Includes previous immunotherapy, chemotherapy, targeted therapy, radiation therapy, prescription medications, over-the-counter medications, and herbal and dietary supplements.

e. Patients with HNSCC must also have HPV and EBV status at Screening or provide historical assessment results.

f. Brain MRI is only required for patients with a history of brain metastases. A standard-of-care brain MRI occurring prior to the 28-day screening window may be acceptable based on consultation with the Medical Monitor.

g. See Section 7.13. Screening and End of Treatment physical examinations will be a complete physical examination. Symptom-directed physical examinations should be performed at the discretion of the Investigator to identify changes from baseline or to evaluate changes based on the patient's clinical symptoms during other clinic visits. The patient's height is measured at the Screening visit.

h. The dose does not need to be recalculated for weight changes that are < 10% from baseline (Day -7).

i. Vital signs to be recorded include temperature, pulse, respiration, systolic and diastolic blood pressure, and oxygen saturation (PaO_2). PaO_2 monitoring is required only at Screening and on dosing days. Collect vital signs before PK sample collection when both vital signs and PK samples are scheduled for the same timepoint, except EOI timepoint. CCI [redacted]

j. An echocardiogram or MUGA or nuclear scan for cardiac function and measurement of LVEF is required prior to dosing and may have been obtained within 60 days prior to C1D1.

k. On C1D1 and C2D1, ECGs are required predose and end of NKTR-255 infusion. All other timepoints, collect ECGs predose. Patients must be resting quietly in the supine position for ≥ 5 minutes prior to collection of 12-lead ECG.

l. For women of childbearing potential (WCBP) only, perform a serum beta subunit of human chorionic gonadotropin (β-HCG) pregnancy test at Screening within 10 to 14 days prior to dosing, and urine or serum pregnancy test within 24 hours prior to day of dosing NKTR-255 on C1D1. In subsequent cycles, perform urine or serum test once each dosing cycle. A negative result is required prior to dosing. Pregnancy testing is not required for women who are postmenopausal for at least 1 year, or surgically sterile for at least 3 months prior to signing the ICF.

m. See Appendix 4. Central safety laboratory results must be used to determine patient eligibility, with the exception that pregnancy tests are done locally (see Section 7.11); thereafter, central laboratory samples must be obtained prior to each cycle. If local laboratory results are used for retreatment decisions due to timing issues (eg, predose, treatment-related AE management, dose delays, etc.), duplicate central safety laboratory tests must be submitted to the central laboratory.

n. Tests include free or total triiodothyronine (T3) reflex testing if TSH is abnormal.

o. Refer to the Laboratory Manual for sample processing. See Table 7 for detailed sampling timepoints.

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u. NKTR-255 will be administered q21d starting C1D1.

v. Cetuximab will be administered at the recommended dose according to the current local prescribing information, ie, IV weekly. A loading dose of 400 mg/m^2 IV is given as an initial dose, then weekly doses of 250 mg/m^2 IV. On days that NKTR-255 and cetuximab are both dosed, cetuximab should be administered first, CCI

w. Patients will remain on treatment until meeting one of the criteria for discontinuation of treatment in Section 5.2.3.1.


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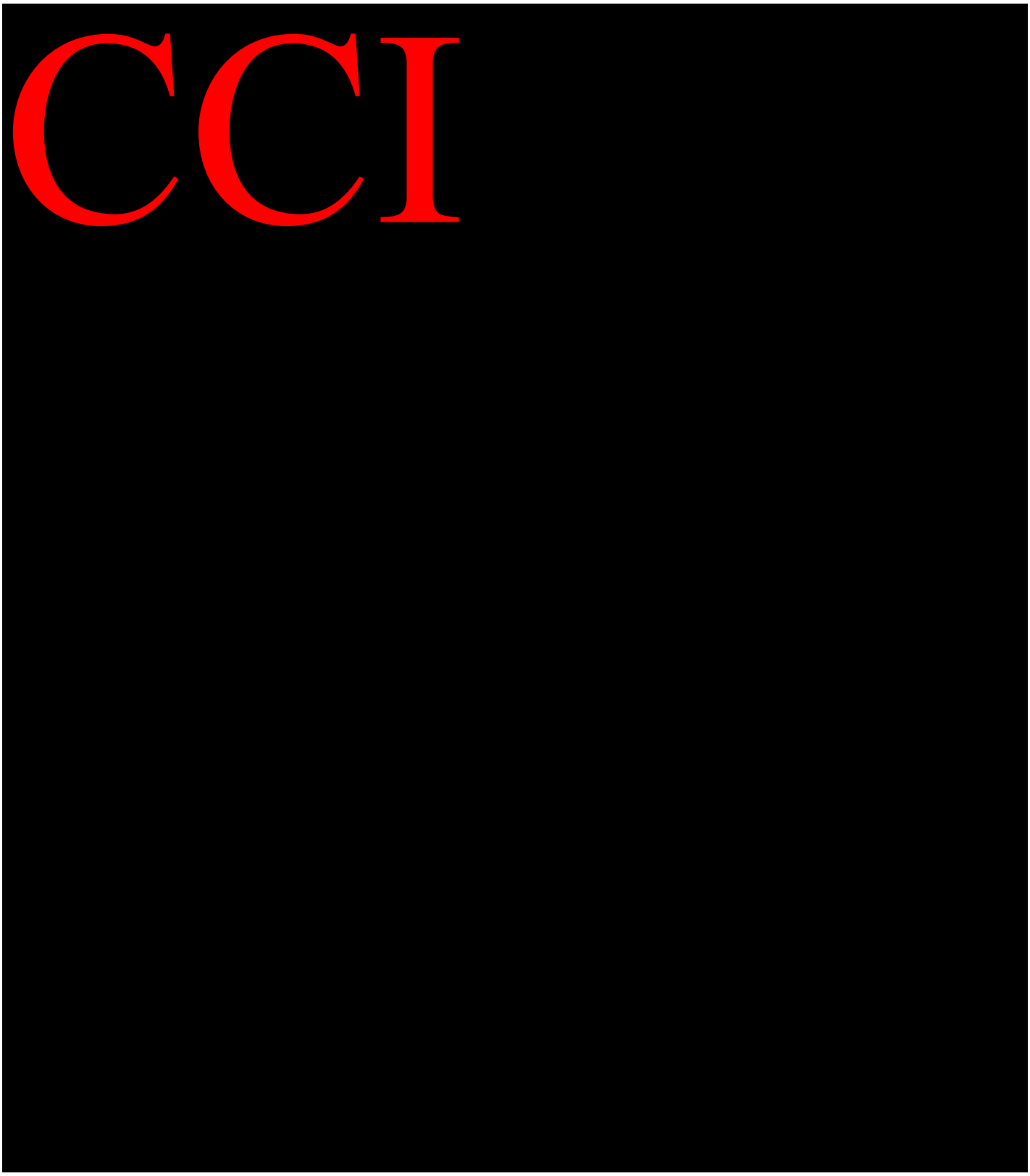
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2.0 INTRODUCTION

2.1 Background

Activating the immune system has been demonstrated to produce durable efficacious responses in human cancers (Hodi, 2010). Targeted monoclonal antibodies (mAbs) that bind to tumor-associated antigens and recruit a patient's immune system to kill the tumor cells via antibody-dependent cellular cytotoxicity (ADCC) are mainstay treatments in oncology. Research on enhancing the immune system to enable functional and numerical capacity of the patient's immune system to synergize with the mAb are coming to focus more recently (Messaoudene, 2017). Because interleukin-15 (IL-15) was initially identified through its ability to mimic interleukin-2 (IL-2)-induced T cell proliferation, the biochemical and functional relation between these cytokines was quickly investigated. The results validated the concept that stimulating T cell and natural killer (NK) cell responses could yield effective and durable responses. IL-15 is a cytokine that has many overlapping functions with IL-2, including the ability to promote anti-tumor responses. IL-15 signaling has been shown in the clinic to stimulate an array of downstream pathways in immune cells leading to increased cellular growth, decreased apoptosis, and enhanced activation and migration of specific immune cells (Conlon, 2015). Endogenous IL-15 plays a crucial role in the development, function, and survival of NK cells, NK T cells, CD8+ T cells, and intestinal intraepithelial lymphocytes (Grabstein, 1994; Berard, 2003; Schluns, 2004).

IL-15 is constitutively expressed by a large number of cell types and tissues, including monocytes, macrophages, dendritic cells, keratinocytes, fibroblasts and nerve cells (Grabstein, 1994). The receptor for IL-15 consists of the α subunit and a common βγ subunit that shares the IL-2 receptor responsible for signal transduction (Giri, 1995). In addition, IL-15 receptor alpha (IL-15Rα) is expressed on antigen-presenting dendritic cells, monocytes, macrophages and lymphocytes. IL-15 signaling also enhances the cytolytic activity of CD8+ T cells and induces long-lasting antigen-experienced CD8+CD44^{hi} memory T cells.

NKTR-255 is a novel immunotherapeutic anti-cancer drug candidate CCI [redacted] The PEG moiety of NKTR-255 serves to extend the effective half-life ($t_{1/2}$) relative to unconjugated rhIL-15. As a result, NKTR-255 is expected to provide sustained IL-15 biological activity without the need for daily dosing. Unlike other engineered IL-15 agents (eg, ALT-803 [Han, 2011]), NKTR-255 binds to IL-15Rα and IL-2/IL-15R βγ subunits and has the potential to maintain the full spectrum of IL-15 biology, including sustained pharmacodynamic (PD) effects of both NK cells and CD8+ memory T cells.

NKTR-255 is being evaluated in hematological malignancies as a salvage regimen in a Phase 1 dose escalation/expansion trial (NCT04136756), testing the safety and efficacy of NKTR-255.

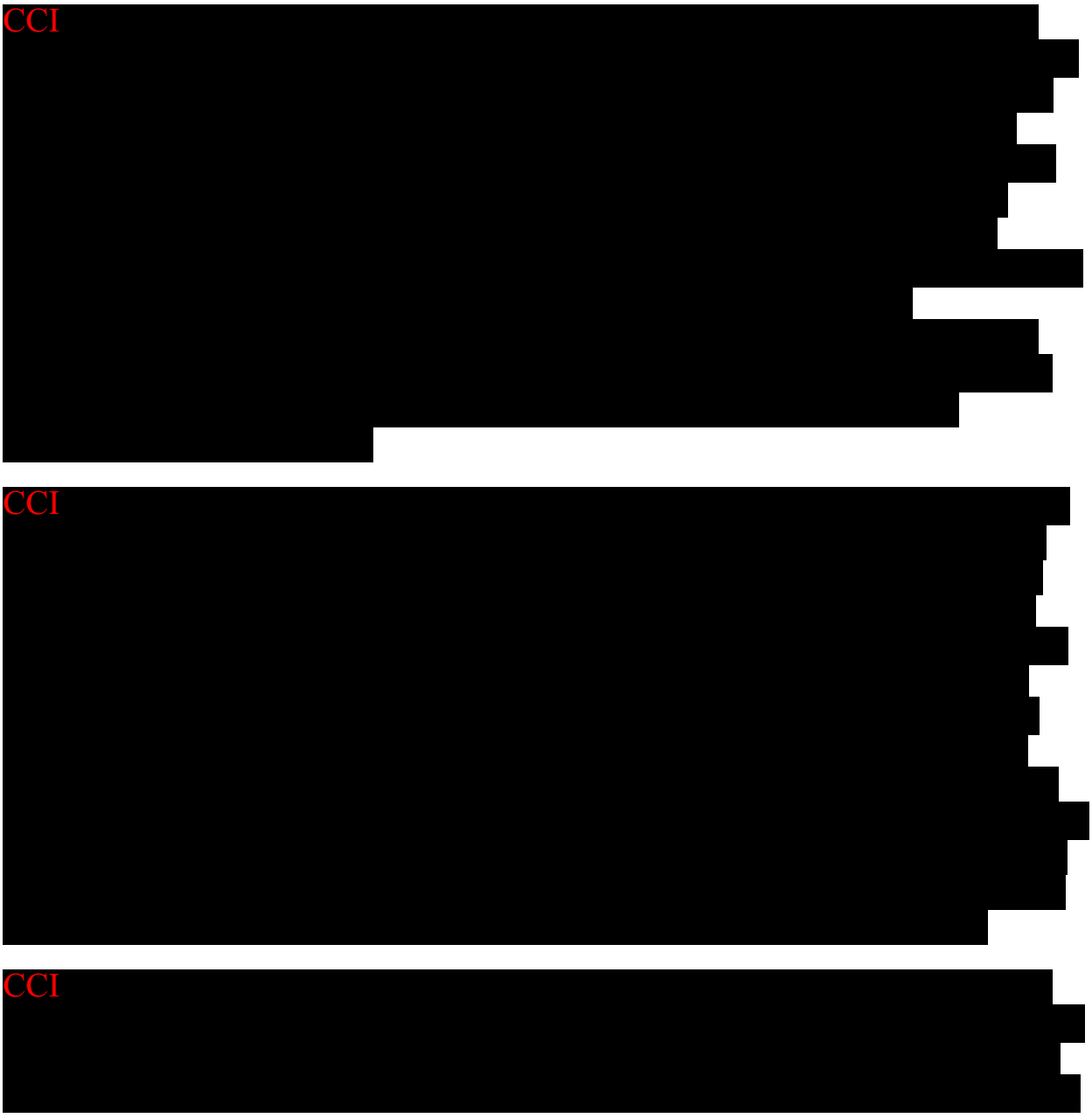
2.1.1 Expansion of NKTR-255 Clinical Development Plan for the Treatment of Solid Tumors

Natural killer cells are innate lymphoid cells endowed with cytolytic activity and a capacity to secrete cytokines and chemokines. Several lines of evidence suggest that NK cells play an important role in anti-tumor immunity by directly lysing tumor cells or through participating in ADCC in conjunction with a tumor targeted monoclonal antibody. High levels of NK cell infiltration have been associated with a better prognosis for some tumors, including solid tumors. However, NK cells are often underappreciated in solid tumors, leading to speculation that these cells might only be involved in the control of hematological malignancies and tumor metastasis (Brittenden, 1996; Halama, 2011). Several studies have shown that the natural cytotoxicity of peripheral blood is significantly lower in patients with solid tumors than in healthy individuals (Brittenden, 1996). More recently, colorectal tumors have been shown to be almost devoid of NK cells, despite efficient T cell infiltration (Halama, 2011).

Squamous cell carcinoma (SCC) accounts for more than 90% of all head and neck cancers and is ranked the sixth most common cancer worldwide, with more than 650,000 new cases and 330,000 deaths reported in 2018 (Vigneswaran, 2014; Bray, 2018). In the United States (US), head and neck squamous cell carcinoma (HNSCC) accounts for 3% of malignancies, with approximately 53,000 Americans developing head and neck cancer annually and 10,800 dying from the disease (Siegel, 2019). The 2 broad approaches to treatment include primary surgery and upfront definitive radiation therapy, either alone or in combination with chemotherapy (Gilbert, 2009). Pembrolizumab has become the new standard first-line treatment either alone or in combination with chemotherapy for patients with metastatic or unresectable, recurrent HNSCC (Rischin, 2019; Keytruda US package insert, 2020). Successful outcomes with pembrolizumab have garnered interest in other immunotherapy modalities as treatment options for HNSCC. Head and neck squamous cell carcinoma is an immunosuppressive disease associated with low absolute lymphocyte count, altered NK cell function, and impairment of tumor-infiltrating T lymphocytes with an important impact on clinical outcome (Ferris, 2004; Kuss, 2004; Dasgupta, 2005). It is therefore of interest to promote NK cell infiltration of tumors and to develop immunotherapeutic approaches designed to harness NK cell functions in the tumor bed, including those that aim to reinforce conventional anti-tumor therapies to increase the chances of successful treatment (Habif, 2019).

Colorectal carcinoma (CRC) is the third most common cancer affecting both males and females in the US; approximately 70% of CRC cases arise in the colon (Siegel, 2019). Globally, CRC is the third leading cause of cancer and cancer-related deaths worldwide (Demb, 2019). The last 15 years have seen major advances in the treatment of metastatic colorectal carcinoma (mCRC). The median survival duration is now approaching 2 years, and 5-year survival rates as high as 15% are reported in some trials of patients treated with chemotherapy alone (Masi, 2011). Cetuximab has emerged as a core agent, along with 5-fluorouracil, irinotecan, oxaliplatin, and bevacizumab, for overall mCRC management and to prolong survival (Lenz, 2007). More recently, antibody to programmed cell death protein 1 (anti-PD-1) agent pembrolizumab received

accelerated approval for the treatment of mismatch repair (MMR)-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. However, microsatellite instability (MSI) is present only in a small subset of CRC patients and has an even lower incidence in the metastatic setting (4%-5%) (Battaglin, 2018). While there is clear clinical evidence for a therapeutic role of immune checkpoint inhibitors such as pembrolizumab, the vast majority of patients with proficient MMR or microsatellite stable tumors do not benefit from immunotherapy (Ciardiello, 2019). Thus, many patients exhaust standard treatment options without deriving benefit and are subsequently transitioned to palliative care even though they still have good performance status.

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2.2 NKTR-255

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2.2.3 Clinical Experience with NKTR-255

NKTR-255 is being evaluated in hematological malignancies as a salvage regimen in a Phase 1 dose escalation /expansion trial (Nektar Study 18-255-02; NCT04136756), testing the safety and tolerability of NKTR-255.

[redacted]

2.2.6 Selection of NKTR-255 Recommended Phase 2 Dose (RP2D)

A composite of clinical information will be used to select the RP2D based on safety and tolerability, PK, PD, and optimal biological response. Additional patients may be enrolled to refine the RP2D and a minimum of 6 patients will be required to define the RP2D.

2.2.6.1 Safety Considerations for NKTR-255 and Cetuximab Combination

Cetuximab is a targeted monoclonal antibody to EGFR and has been part of the treatment backbone for metastatic CRC since its approval in 2004 and for HNSCC since approval in 2006. The safety of cetuximab as monotherapy has been well characterized and summarized by several multicenter clinical studies (Fakih, 2010; Erbitux US package insert, 2021). In this study, the loading dose of cetuximab will be given as monotherapy.

Infusion-related reactions occurred within minutes of administration of cetuximab (median: 15 minutes, range: 2 to 140 minutes). The time from start of cetuximab to onset of IRR correlated inversely with the grade of the IRR, whereby the onset of the IRR occurred much earlier with Grade 4 IRR and later with lower grades of IRR (median to onset of Grades 4, 3, 2, and 1 IRR were 5, 13.5, 22, and 25 minutes, respectively, $p = 0.04$). Pharmacologic prophylaxis with antihistamines IV 30 to 60 minutes prior to the first dose has been shown to be effective in reducing IRR incidence (Touma, 2014).


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3.0 OBJECTIVES

3.1 Primary Objectives

The primary objectives are:

Phase 1b (Dose Escalation):

- To evaluate the safety and tolerability, as well as define the MTD and/or RP2D, of NKTR-255 in combination with cetuximab in relapsed or refractory (R/R) HNSCC CRC

Phase 2 (Dose Expansion):

- To evaluate the safety and tolerability of NKTR-255 monotherapy and NKTR-255 in combination with cetuximab in R/R HNSCC, CRC, CCI
- To evaluate the efficacy of NKTR-255 in combination with cetuximab in R/R HNSCC or CRC by assessing the ORR by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1)

3.2 Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of NKTR-255 monotherapy in R/R CCI by assessing the ORR by RECIST 1.1
- To evaluate the efficacy of NKTR-255 in combination with cetuximab and NKTR-255 monotherapy by assessing progression-free survival (PFS) and overall survival (OS)

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4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

4.1.1 Inclusion Criteria for All Patients

Each patient must satisfy all of the following criteria to be enrolled in the study (for both dose escalation and dose expansion phases):

1. Patients must be at least 18 years of age at study entry, and of any gender, race, or ethnicity.
2. Patients must be capable of understanding and providing a written informed consent.
3. Women of childbearing potential (WCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) at Screening and a negative serum or urine pregnancy test within 24 hours prior to dosing. Women of childbearing potential and men who are sexually active with WCBP must commit to use contraception as described in Appendix 7, for the duration of the study and for 1 month after the last dose of NKTR-255 and 2 months after the last dose of cetuximab.
4. Histologically confirmed diagnosis of a locally advanced (not amenable to curative therapy such as surgical resection or radiotherapy) or metastatic cancer of the following histologies: HNSCC, CRC, CCI [redacted]
5. Patients who have previously received cetuximab or other EGFR-directed therapies are excluded from Phase 2 of the trial, unless cetuximab was given as part of a primary treatment approach, with no progressive disease for at least 4 months following the end of prior cetuximab treatment.
6. Life expectancy > 12 weeks as determined by the Investigator
7. Eastern Cooperative Oncology Group performance status 0 or 1 (Appendix 5)
8. Measurable disease per RECIST 1.1
9. Patients must have demonstrated adequate organ function within 14 days before Cycle 1 Day 1 (C1D1):
    a. Estimated glomerular filtration rate ≥ 40 mL/min/1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (see Appendix 6)

4.1.2 Inclusion Criteria for Specific Tumor Types

A patient may be entered into this study only if he/she meets all of the following additional criteria specific to that patient's tumor type:

- Head and Neck Squamous Cell Carcinoma

1. Patients must have histologically or cytologically confirmed advanced, recurrent, or metastatic HNSCC that could not be treated with curative intent. “Advanced” is defined as either locally advanced HNSCC not amenable to curative surgery or radiotherapy or with distant metastases.
2. Patients who have undergone treatment with anti-PD-1 or antibody to programmed death-ligand 1 (anti-PD-L1) (together termed "anti-PD-(L)1") must have had the last dose of antibody at least 4 weeks prior to receiving any study drug and evidence of tumor progression before they can be enrolled into this study.
3. Patients must have known status by pathology for HPV and Epstein-Barr virus (EBV) in HNSCC, either metastatic or recurrent disease.
4. Patients must have experienced progression (or toxicity precluding additional treatment) on any first- or second-line platinum-based chemotherapy and anti-PD-(L)1 antibody, unless they are ineligible for such treatment, **OR**,
5. Patients must be ineligible for platinum-based (either cisplatin or carboplatin) chemotherapy or chemoradiation due to decline in renal function and/or patient's intolerance.

- Colorectal Cancer

1. Patients must have a histologically or cytologically confirmed diagnosis of advanced CRC; patients in Phase 2 must have confirmed *KRAS* (US) or *RAS* (ex-US) wild type EGFR-expressing advanced CRC. “Advanced” is defined as either locally advanced unresectable cancer or metastatic disease.
2. Patients must have received at least 2 prior cancer therapy regimens administered for metastatic disease including fluoropyrimidine, irinotecan, and oxaliplatin, unless ineligible or intolerant for such treatment.
3. Patients with MSI-H or dMMR tumors must have been exposed to checkpoint inhibitors such as anti-PD-1.

4.2 Exclusion Criteria

Patients who meet any of the following criteria are ineligible:

1. Use of an investigational agent or an investigational device within 28 days before administration of first dose of study drug(s)
2. 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 corticosteroids 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, chronic graft-versus-host disease, Graves' disease, Hashimoto's disease, alopecia areata, eczema, psoriasis, or with Medical Monitor approval).
3. History of allergy or known hypersensitivity to murine protein or study drug components
4. History of organ transplant that requires ongoing use of immunosuppressive agents
5. Patients who have been previously treated with IL-2 or IL-15

6. Patients with HNSCC who require treatment with anticoagulation therapy are not eligible. Use of warfarin for CRC, CCI [redacted] patients within 14 days of initiating study drug(s) is not permitted. Additional information about anti-coagulant therapy on treatment can be found in Section 5.10.3.
7. Known Grade 3 or 4 hypersensitivity reaction to cetuximab, history of allergy to red meat or tick bites, or history of positive test results for immunoglobulin E antibodies against cetuximab
8. Patient has had prior Grade 4 IRR to cetuximab
9. Unresolved toxicity from previous anti-cancer therapy, unless resolved to Grade ≤ 1 or baseline; or resolved to Grade 2 (with the exceptions outlined in the inclusion criteria or deemed clinically not significant, and approved by the Sponsor); or resulting from incomplete recovery from recent surgery (major)
10. Prior surgery or radiotherapy within 14 days of initiating study drug(s). Patients must have recovered from all acute radiation-related toxicities, not require corticosteroids, and have not had radiation pneumonitis.
11. Patients participating in observational studies should be discussed with the Medical Monitor to confirm eligibility.
12. Patients who have had < 28 days since the last anti-cancer treatment, chemotherapy, or biological therapy, or < 14 days from approved tyrosine kinase inhibitor therapy (sunitinib, sorafenib, vemurafenib, dabrafenib, cobimetinib), or systemic or inhaled steroid therapy at doses greater than 10 mg of prednisone or equivalent before administration of the first dose of study drug(s)
13. Patients who have received systemic interferon alpha (IFNα) within the previous 6 months prior to enrollment in the study are not eligible.
14. Active infection requiring systemic therapy within 7 days prior to dosing
15. Evidence of clinically significant interstitial lung disease or active, noninfectious pneumonitis
16. Known immunodeficiency or active HIV (antibodies to HIV-1 or HIV-2). However, HIV-associated ASCC patients on effective anti-retroviral therapy with CD4+ count ≥ 300/μL and undetectable viral load are eligible.
17. Known to be seropositive or active for hepatitis B or hepatitis C as defined in Section 5.13.6. Patients who had hepatitis B but have received an antiviral treatment and show non-detectable viral DNA for 3 months are eligible. Patients who are seropositive because of hepatitis B virus vaccine are eligible.
18. Prolonged Fridericia's corrected QT interval (QTcF) > 450 ms for men and > 470 ms for women at Screening
19. History of unstable or deteriorating cardiac disease within the previous 6 months prior to Screening including but not limited to the following:

a. Unstable angina or myocardial infarction

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

c. Uncontrolled clinically significant arrhythmias

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

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21. Patient has any of the following laboratory test results during Screening:

a. Aspartate aminotransferase or ALT level ≥ 2.5 × the upper limit of normal (ULN)

b. Alkaline phosphatase level ≥ 2.5 × ULN

c. Total bilirubin level ≥ 2 × ULN (except for Gilbert Syndrome: direct bilirubin ≥ 2 × ULN)

d. Potassium level < 3.0 mEq/L; or > 10 mEq/L

e. Corrected serum calcium > 14.0 mg/dL (3.5 mmol/L)

f. Magnesium level < 1.0 mg/dL

22. Patient is a woman who is pregnant or breastfeeding or planning to become pregnant while enrolled in this study or within 1 month after the last dose of NKTR-255 or within 2 months after the last dose of cetuximab.

23. 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 study treatment). There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 4 weeks prior to study treatment. Stable dose of anticonvulsants is required within 14 days prior to study treatment. Treatment for central nervous system metastases may include stereotactic radiosurgery (eg, GammaKnife, CyberKnife, or equivalent) or neurosurgical resection. Patients who received whole brain radiation therapy are not eligible.

24. History of unstable hypertension and/or Screening blood pressure > 150/90 millimeters of mercury (mmHg) (systolic/diastolic) with or without end organ damage; Screening blood pressure must be < 150 mmHg for systolic blood pressure and < 90 mmHg for diastolic blood pressure (by at least 1 and up to 3 observations taken during the Screening period).
25. Live, attenuated vaccines are prohibited within 30 days before the first dose of study drug (exception is made for vaccines against severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]; coronavirus disease 2019 [COVID-19]). For details, refer to Section 5.10.3.
26. Known current drug, alcohol, or tobacco abuse
27. Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol

5.0 INVESTIGATIONAL PLAN

5.1 Overview

This study is a Phase 1b/2, open-label, multicenter, dose escalation, and dose expansion study in patients with R/R HNSCC, CRC, CCI [redacted].

5.1.1 Phase 1b – Dose Escalation

The NKTR-255 starting dose will be 1.5 µg/kg, which had no safety concerns as defined by pre-specified dose-limiting toxicities (DLTs) in the first cohort of the FIH study Protocol 18-255-02. The starting dose is based on the safety data from escalation cohorts and the RP2D determination from the FIH study. The starting dose will not be greater than the highest dose determined by the Safety Review Committee (SRC) to have no safety concerns in the FIH study.

After an initial cetuximab loading dose, patients will receive IV NKTR-255 q21d in combination with cetuximab weekly (Figure 2). Beginning with Dose Level 1, successive dose levels of at least 3 patients each will receive ascending doses of NKTR-255 until the MTD and/or RP2D is determined. Approximately 30 patients may be enrolled in the dose escalation phase of the study. A 2-parameter Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle (Neuenschwander, 2008) will be used as a guide during the escalation phase of the study for dose level selection and for determination of the MTD and/or RP2D. Additional dose levels may also be opened to further explore the MTD and/or RP2D. For details, refer to Sections 5.8 and 5.9.

The first patient (a sentinel patient) of each escalating NKTR-255 dose level will be monitored for safety and tolerability for 7 days after the first dose of NKTR-255 before additional patients are dosed within the same dose level.

A composite of clinical information will be used to select the RP2D based on safety and tolerability, PK, CCI and optimal biological response. Additional patients may be enrolled to refine the RP2D, and a minimum of 6 patients will be required to define the RP2D.

Eligible patients will receive cetuximab 400 mg/m^2 IV as a loading dose during the study run-in period (Day -7). Thereafter, cetuximab 250 mg/m^2 IV will be administered weekly and NKTR-255 will be administered q21d. The DLT window is 21 days after the first dose of NKTR-255. Patients who achieve optimal response (partial response [PR] or complete response [CR] as determined by RECIST 1.1) after at least 1 tumor assessment, as determined by the Investigator and in consultation with the Medical Monitor, will be given the option to continue treatment with NKTR-255 as single agent for maintenance every 28 days (q28d) at the same dose as the patient's originally assigned dose.

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- Intermediate doses may be evaluated.
- No intra-patient dose escalation will be allowed.
- Enrollment into a new dose level with an escalating dose of NKTR-255 cannot begin until the DLT window has closed for at least 3 patients in the prior dose level. The DLT window is 21 days after the first dose of NKTR-255.
- The SRC will assess safety before opening dose escalation to the next level.
- The Sponsor's decision to declare the RP2D of NKTR-255 can occur at any given dose level based on safety, PK or CCI effects without reaching the MTD.
- Data from a minimum of 6 evaluable patients are required to define the RP2D.
- Dose reduction of NKTR-255 is not allowed during dose escalation within the DLT window. Outside of the DLT window in the dose escalation phase, and during dose expansion, dose levels of NKTR-255 may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested (the dose level may be de-escalated in order to characterize RP2D for a specific dose).
- The cetuximab dose may be reduced or adjusted based on review of available safety and tolerability data. Dose adjustment or discontinuation for cetuximab may be required based on emerging toxicities, and should follow the guidelines specified in this protocol and in the current local prescribing information for cetuximab.

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5.2 Study Periods

5.2.1 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 of care. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (eg, full physical examination) as long as the procedures were completed within the window of that assessment during the Screening period (Section 1.2). After signing the informed consent form (ICF), patients will be evaluated for all eligibility criteria during the Screening period before administration of study drug(s). Rescreening after screen failure will be allowed after consultation with the Medical Monitor. The Screening window is 28 days. Baseline scan(s) available up to 14 days prior to signing the ICF are acceptable.

5.2.2 Assigning Patient Numbers

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

5.2.3 Treatment Period

Patients will remain on treatment until meeting one of the criteria for discontinuation of treatment in Section 5.2.3.1. In the event of a patient's withdrawal, the Investigator will promptly notify the Sponsor and make every effort to complete the End of Treatment (EOT) procedures specified in the Schedule of Events (Section 1.2). Patients will continue to be followed for safety and survival as per Sections 5.2.6 and 5.2.7, respectively.

If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. The allowable windows for PK and immunogenicity sampling, and vital signs on PK collection days is provided in Table 6. All out-of-window visits and procedures will incur a protocol deviation.

Patients will remain on study until meeting one of the criteria for discontinuation of study in Section 5.2.3.3. Patients may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment.

Patients in Phase 1b (dose escalation) or Phase 2 Cohorts A, B, C1, D1, and/or E1 who achieve an optimal response (CR or PR per RECIST 1.1) after at least 1 tumor assessment, as determined by the Investigator and in consultation with the Medical Monitor, may transition to a q28d schedule of single-agent NKTR-255 as maintenance at the same dose as the patient's originally assigned dose.

Patients receiving monotherapy NKTR-255 who do not achieve optimal response will have the option to receive cetuximab add-on.

See Section 5.2.5 for information about treatment beyond progression.

5.2.3.1 Criteria for Discontinuation from Treatment

Study treatment may be discontinued for any of the following reasons:

- Any clinical AE, laboratory abnormality, or intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree
- Toxicity that, despite maximum medical management, in the judgment of the Investigator, compromises the ability to continue study-specific procedures or is considered to not be in the patient's best interest
- Disease progression (based on Investigator assessment of baseline and post-baseline scans as per RECIST 1.1). In some circumstances patients may be treated beyond disease progression. Details are provided in Section 5.2.5.
- Patient request to discontinue treatment for any reason
- Patient noncompliance
- Initiation of systemic antineoplastic therapy other than treatments per protocol in the absence of progression
- Discontinuation of the study treatment at the request of Nektar, a regulatory agency or an institutional review board (IRB) or independent ethics committee (IEC)
- Pregnancy during treatment
- Death
- Investigator's decision, in consultation with the Medical Monitor

If a patient discontinues NKTR-255, the patient may continue on cetuximab alone, at the discretion of the Investigator, until disease progression or initiation of systemic anti-tumor therapy (whichever is earlier).

If a patient discontinues study drug(s), every attempt should be made to continue tumor assessment at every 9 weeks until disease progression or initiation of systemic anti-tumor therapy. The patient will be asked to attend the 60-day post-treatment follow-up assessment visit when discontinuing from the study treatment.

5.2.3.2 End of Treatment Visit

Patients will remain on study until meeting one of the criteria for discontinuation of study in Section 5.2.3.3. Patients who are discontinued will complete the EOT visit and all safety follow-up procedures as per the Schedule of Events (Section 1.2). The EOT visit should occur

within 7 days after study treatment is discontinued, and before a new antineoplastic regimen has been initiated.

5.2.3.3 Criteria for Discontinuation from Study

Patients who discontinue study treatment due to any of the treatment discontinuation criteria in Section 5.2.3.1 will continue to be followed for survival per Section 5.2.7.

In the event of an unscheduled study termination by the Sponsor, patients who are on-treatment at the time of the end of the study will be followed for safety for 60 days post EOT as per Section 5.2.6.

Criteria for study discontinuation may include:

- Withdrawal of consent from study
- Loss to follow-up
- Death
- Discontinuation of the study at the request of Nektar, a regulatory agency or an IRB/IEC
- Principal Investigator's decision
- Medical Monitor's assessment due to lack of adherence to protocol

5.2.3.4 Replacement of Patients

In the dose escalation portion, patients who do not complete the DLT observation period for reasons other than a DLT may be replaced to provide a sufficient number of patients for adequate evaluation of each dose escalation level.

Patients will not be replaced during the dose expansion portion of the study.

5.2.4 Maintenance Period

Patients in Phase 1b (dose escalation) CCI [redacted] who achieve optimal response (PR or CR per RECIST 1.1) after at least 1 tumor assessment, as determined by the Investigator and in consultation with the Medical Monitor, will be given the option to continue treatment with NKTR-255 as single agent for maintenance q28d at the same dose as the patient's originally assigned dose.

5.2.5 Treatment Beyond Progression

Accumulating evidence indicates that some patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease. Patients will be permitted to continue on treatment beyond progressive disease as long as they meet the following criteria:

- Investigator-assessed clinical benefit.
- Continue to meet all other study protocol eligibility criteria.
- Patient tolerates study drug(s).
- No clinical signs or symptoms of disease progression or clinical deterioration.
- Patient has stable ECOG performance status of ≤ 2.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, central nervous system metastases).

The assessment of clinical benefit should take into account whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the Medical Monitor, and an assessment of the risk/benefit of continuing with study drug(s) must be documented in the patient records. Patient will sign a "treatment beyond progression ICF" prior to continuing.

5.2.6 Safety Follow-up

The Safety Follow-up visit should occur 60 days after the last dose of study treatment unless the patient withdraws consent to treat, initiates new anti-cancer therapy, is lost to follow up, or death occurs. In case of a clinically significant AE, the patient will be followed for safety until resolution, return to baseline values, or permanent sequelae of all toxicities attributable to study drug(s). If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or until the event is considered to be stable and/or chronic.

5.2.7 Survival Follow-up

Following discontinuation of study treatment, patients will be contacted approximately every 3 months ± 14 days after the EOT by clinic visit or telephone, or other alternate methods such as email, contact with family, or public records (if allowed per local regulations), to obtain the information about alternative anti-cancer therapy and assess survival information until the patient meets the criteria for study discontinuation in Section 5.2.3.3.

5.2.8 End of Study

End of study is defined as no more than 2 years after the last patient received his or her last dose of NKTR-255 or Sponsor decision to terminate the study, whichever comes first.

At the conclusion of the study, patients who continue to demonstrate clinical benefit may be able to receive Nektar-supplied study treatment for a maximum treatment duration of 2 years. NKTR-255 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: 1) a study is terminated due to safety concerns; 2) the development of NKTR-255 is terminated for other reasons, including but not limited to, lack of efficacy and/or not meeting the study objective; 3) the patient can obtain medication from a government sponsored or private health program. In all cases Nektar will follow local regulations.

5.3 Administration of Study Drug(s)

5.3.1 NKTR-255 Dosing

Dose administration is shown in Figure 2 and Figure 3. NKTR-255 will be administered as a 30-minute infusion, q21d as monotherapy and in combination with cetuximab, and q28d as single-agent maintenance at the same dose as the patient's originally assigned dose. For applicable dose levels or cohorts (Phase 1b CCI), cetuximab will be given weekly. CCI

The dose does not need to be recalculated for weight changes that are < 10% from baseline (Day -7).

CCI

CCI

5.3.1.4 NKTR-255 Monotherapy with Cetuximab Add-On

Patients in Cohorts C, D, E, A1, and B1 (monotherapy cohorts) who, after at least 1 tumor assessment, do not experience PR or CR per RECIST 1.1, will have the option to receive cetuximab as "add-on" therapy. Patients opting to receive NKTR-255 in combination with cetuximab will maintain their original cohort assignment.

Patients will receive a loading dose of cetuximab 400 mg/m^2 IV 7 days prior to their next scheduled cycle of NKTR-255 and thereafter cetuximab will be administered at a dose of 250 mg/m^2 IV weekly.

Patients in the "add-on" treatment group will be assessed, monitored, and treated as per Table 5. All other portions of the protocol applicable to patients receiving NKTR-255 in combination with cetuximab are applicable to these cetuximab add-on patients as well.

5.3.1.5 NKTR-255 Dose Delay and Adjustment Criteria

NKTR-255 dose adjustments may only be performed with approval of the Sponsor's Medical Monitor. Dose adjustments of NKTR-255 within a single patient are not permitted within the DLT window. Outside of the DLT window in the dose escalation phase and during dose expansion, dose levels of NKTR-255 may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested (the dose level may be de-escalated in order to characterize RP2D for a specific cohort).

NKTR-255 doses may be delayed or reduced per the recommendation of the Investigator and approval of the Sponsor's Medical Monitor, based on observed drug-related toxicities for the following reasons:

- Grade 1 or 2 toxicity: No requirement for dose delay or dose reduction. If the toxicity persists at Grade 2 following completion of the cycle, a dose delay or dose reduction may be implemented in consultation with the Medical Monitor.
- Grade 3 toxicity: NKTR-255 may be withheld if toxicity cannot be managed by adequate medical intervention. NKTR-255 dosing may resume at one dose level lower 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.
- Grade 4 non-hematological toxicity that is not considered by the Investigator to be attributable to another identifiable cause: dosing should be permanently discontinued.
- For specific severe or medically important toxicities that require permanent treatment discontinuation, refer to Section 5.7.

Tumor assessments for all patients should continue as per protocol even if dosing is delayed. Grading of AEs is described in Section 7.3.

5.3.1.6 Criteria to Resume NKTR-255

Patients will be permitted to resume study drug(s) at the same dose level(s) following resolution of the AE to Grade ≤ 1 or to baseline within 2 weeks after the completion of the prior cycle, with the exception of patients who meet criteria for permanent discontinuation as specified in Section 5.7.

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

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT **or** total bilirubin.
- Patients with combined Grade 2 AST/ALT **and** total bilirubin values meeting discontinuation parameters (see Section 5.7) should have treatment permanently discontinued.

A dosing delay lasting more than 2 weeks should be discussed with the Medical Monitor and the patient may resume the study if approved based on clinical assessment.

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.

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

5.3.2 Cetuximab Dosing

In Phase 2 (Dose Expansion), cetuximab will only be administered in Cohorts A, B, C1, D1, and E1, and in patients in the monotherapy cohorts (Cohorts C, D, E, A1, and B1) who, after at least 1 tumor assessment, do not experience PR or CR per RECIST 1.1. In these patient groups, cetuximab 400 mg/m^2 IV will be given alone as a loading dose 7 days before the start of Cycle 1 (Day -7). Starting C1D1, cetuximab 250 mg/m^2 IV will be administered once weekly. CCI [redacted]

Body surface area used in calculating cetuximab dose should be the same as the Day -7 value, unless there is a ≥ 10% change in weight or height of the patient in which case the body surface area will be re-calculated based on the new weight and height of that patient within a cycle.

For current information about administration and dose modification of cetuximab refer to the current local prescribing information, published on the local applicable website (eg, http://base-donnees-publique.medicaments.gouv.fr).

The cetuximab dose may be reduced or adjusted based on review of available safety and tolerability data. Dose adjustment or discontinuation for cetuximab may be required based on emerging toxicities and should follow the guidelines specified in this protocol and in the current local prescribing information for cetuximab.

For Grade 1 or 2 IRRs, the infusion rate may be reduced by 50%. For Grade 3 or 4 IRRs, cetuximb must be immediately and permanently discontinued.

For additional information about cetuximab administration, refer to the current local prescribing information.

5.4 Determination of Dose-Limiting Toxicities (DLTs)

Clinically relevant toxicities will be those assessed as unrelated to disease, disease progression, intercurrent illness, or concomitant medications. These will be evaluated according to the National Cancer Institute/National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE). Dose-limiting toxicities will be assessed during the predefined DLT window (Section 5.5).

5.5 Dose-Limiting Toxicity Observation Period

Dose-limiting toxicities will be assessed during the dose escalation and dose expansion portions of the study. The DLT window will be 21 days after the first dose of NKTR-255.

Enrollment into a new dose level with an escalating dose of NKTR-255 may not begin until the DLT window has closed for at least 3 patients in the prior dose level. The dose escalation scheme is described in Section 5.1.

5.5.1 Dose-Limiting Toxicities Related to NKTR-255 and Cetuximab

Examples of AEs related to NKTR-255 or NKTR-255 combined with cetuximab that are defined as a DLT include the following:

1. Any Grade ≥ 3 non-hematological AE except those listed in Section 5.5.2
2. Any Grade 4 hematological AE, including neutropenia, leukopenia, thrombocytopenia, and anemia, except those listed in Section 5.5.2
3. Any Grade 3 thrombocytopenia with bleeding
4. Any case meeting the Hy's law criteria (https://www.fda.gov/downloads/Guidances/UCM174090.pdf)
5. Any Grade ≥ 3 (> 5x ULN) AST/ALT elevation

6. Any Grade ≥ 3 (> 3x ULN) total bilirubin elevation
7. Any Grade 4 nausea or vomiting
8. Any Grade 4 amylase or lipase elevation
9. Death not clearly due to underlying disease or extraneous causes or disease progression

Laboratory findings indicating a DLT should be reconfirmed by the local laboratory within 24 hours.

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

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

1. Lymphopenia < 14 days in duration or not associated with clinical manifestations
2. Grade 3 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
3. Tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor
4. Grade 3 nausea or vomiting that can be medically managed to Grade ≤ 2 within 72 hours
5. Fatigue that improves to Grade ≤ 2 within 7 days
6. Grade 3 rash that improves to Grade ≤ 2 within 7 days
7. Grade 3 amylase or lipase not associated with symptoms or clinical manifestations of pancreatitis.

5.5.3 Delayed Dose-Limiting Toxicities

Delayed DLTs are AEs as defined in Section 5.5.1 that occur after the predefined DLT window. Delayed DLTs will be collected and evaluated by the Investigator and the Medical Monitor on an ongoing basis and also reviewed by the SRC. Delayed DLTs will also be reviewed in context of the determination of the MTD.

5.5.4 Proposed Stopping Rules

Dose-limiting toxicities will be monitored by the SRC during the dose escalation and dose expansion. Study enrollment may be suspended based on calculated DLT rate listed below. Table 11 below is provided as a reference for the suspension boundaries. Patients will be monitored across doses and cohorts after a minimum of 6 patients have been treated. The reference suspension boundaries due to toxicity are based on a Bayesian sequential monitoring design (Thall, 1995) with the following criterion:

$$\Pr[\text{prob}(\text{NKTR-255 related DLT}) > 0.33 \mid \text{data}] > 0.95$$

A beta (0.66, 1.34) prior distribution is assumed for the toxicity rate, which has a mean of 0.33 corresponding to the 33% target toxicity rate. If there is a greater than 95% chance that the DLT rate is greater than 33%, accrual will be suspended and the SRC will meet to review safety data including aggregated safety summaries. Table 12 below presents the operating characteristics of the above monitoring rule.

Table 11: Suspension Boundaries for Toxicity

Number of Safety Evaluable Patients	Suspending Accrual if ≥ Number of Patients Observed with NKTR-255-related DLTs	Number of Safety Evaluable Patients	Suspending Accrual if ≥ Number of Patients Observed with NKTR-255-related DLTs
1–5	Not Applicable	42–44	20
6–7	5	45–46	21
8–9	6	47–49	22
10–12	7	50–51	23
13–14	8	52–54	24
15–16	9	55–57	25
17–19	10	58–59	26
20–21	11	60–62	27
22–23	12	63–65	28
24–26	13	66–67	29
27–28	14	68–70	30
29–31	15	71–73	31
32–33	16	74–75	32
34–36	17	76–78	33
37–38	18	79-81	34
39–41	19	82-83	35
—	—	84	36

DLT = dose-limiting toxicity

Table 12: Operating Characteristics of Suspension Boundaries for Toxicity

	True Toxicity Incidence					
Early Stopping Probability	**0.15**	**0.25**	**0.30**	**0.33**	**0.45**	**0.60**
N < 84	0.00	0.04	0.11	0.21	0.86	1.00
N < 60	0.00	0.03	0.11	0.19	0.76	1.00
N < 48	0.00	0.03	0.10	0.17	0.68	0.99
N < 24	0.00	0.03	0.08	0.13	0.46	0.90
Average Sample Size	83.9	81.6	77	71.8	36.1	12.6

5.6 Safety Review and Data Monitoring

An SRC will be used for the dose escalation and dose expansion phases of the study. The SRC will be comprised of at least one site Investigator and the Sponsor's Medical Monitor. Additional patients may include representatives from the Sponsor's Clinical Development, Drug Safety, Biostatistics, and Clinical Pharmacology divisions as well as other functional representatives as needed to review safety data. For dose escalation levels, the SRC will jointly assess safety before opening dose escalation to each level. The exact dose will be confirmed based on review of safety data after at least 3 patients have been enrolled in each level.

An independent, external, and multidisciplinary Data Safety Monitoring Committee (DSMC) composed of 3 to 5 members will be established and include at least 1 clinician knowledgeable in the field of the trial and at least 1 statistician. The DSMC will operate according to a prespecified charter and make recommendations on study conduct related to patient safety. The DSMC will review the progress of the study and perform reviews of safety data and provide recommendation to whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the patients, whether the study should continue as planned, or whether the study should continue with modifications.

5.7 Permanent Treatment Discontinuation Criteria

Patients meeting any of the following criteria will be required to permanently discontinue all assigned study drug(s). However, with Medical Monitor approval, NKTR-255 treatment may continue if the toxicities listed below are considered related to cetuximab only.

- Progressive disease per RECIST 1.1 (see details regarding continuing treatment beyond initial assessment of progression, Section 5.2.5)
- Clinical deterioration, as assessed by the Investigator
- Grade 3 or 4 CRS (Lee, 2014)
- Grade 3 or 4 IRR
- Grade 4 rash

- Grade 3 laboratory abnormalities require treatment discontinuation for the following:
  - Grade 3 thrombocytopenia > 7 days associated with clinically significant bleeding requires discontinuation.
- Any Grade 4 AE or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - 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
- Any AE, laboratory abnormality, or intercurrent illness, which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued treatment.
- Any dosing delay lasting > 2 weeks after completion of the prior cycle, with the following exceptions (see Section 5.3.1.5 for dose delay and adjustment criteria):
  - Patient has not started any new therapy.
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Tumor assessments should continue as per protocol even if dosing is delayed.
  - The Investigator and the Medical Monitor may agree to a longer dose delay following a clinically significant AE if the patient is deriving clinical benefit from the regimen as defined by CR, PR, or stable disease, up to 6 weeks from last dose of either of the 2 investigational agents, per RECIST 1.1. Any delay beyond 6 weeks must be discussed with the Medical Monitor and approval documented.

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 (see Section 5.11).

5.8 Dose Escalation Decision Criteria

After the completion of the DLT observation period of the last patient enrolled in a dose escalation level, the BLRM will be re-run to obtain updated posterior probabilities of under-dosing, targeted toxicity, and excessive toxicity (see Appendix 1) for all doses. The model-recommended dose for the next dose level of patients will thus be computed in steps (a) through (c) below:

a) identify the range of doses that satisfy the EWOC criteria and are ≤ 100% increment from the current dose

b) identify the dose that has the highest posterior probability of targeted toxicity from the range of doses from a) above

c) adjust the dose from b) above based on criteria C1–C8 as defined in Appendix 1.

The dose recommended by the adaptive Bayesian logistic model will be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of the analysis in determining the next dose level to be investigated. Generally, the study will not treat patients at a dose higher than the model-recommended dose. However, the study may escalate to or stay at a dose higher than the model-recommended dose if such a decision is consistent with accepted clinical practice (eg, standard 3+3 escalation rules serving as guidance). The dose given to the next dose level in the study will be based on considerations of the MTDs estimated by the BLRM. The overall clinical assessment of all available safety and tolerability, PK, and PD data may also be taken into consideration for the determination of dose given to the next dose level.

5.9 Determination of MTD

Definition of MTD:

The MTD is the highest NKTR-255 dosage in combination with cetuximab that is not expected to cause a DLT in more than 33% of the treated patients in the DLT window of NKTR-255. Adverse events and laboratory abnormalities considered to be DLTs are defined in Section 5.5.

Estimation of MTD:

A 2-parameter BLRM employing the EWOC principle (Babb, 1998; Neuenschwander, 2008) will be used during the escalation phase for selection of NKTR-255 doses to investigate and for estimation of the MTD of NKTR-255 when used in combination with cetuximab. The general plan is that dose levels of patients will receive escalating doses of NKTR-255 in combination with cetuximab until the MTD or approximately 30 patients are dosed (see Section 5.1). Estimation of the MTD during the escalation phase of the study will be based upon the estimation of the probability of DLT in Cycle 1. The corresponding methodology is described in Section 5.1 and Appendix 1.

5.10 Prior and Concomitant Medications

5.10.1 Permitted Medications

Premedication for IRRs is not permitted for the first dose of NKTR-255.

Treatment for flu-like symptoms with either acetaminophen or ibuprofen (or equivalent) is permitted for patients receiving NKTR-255 per the Investigator's discretion.

Treatment for flu-like symptoms with antihistamines is permitted for patients receiving NKTR-255 per the Investigator's discretion.

Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). A brief (less than 3 weeks) course of

corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

5.10.2 Permitted Cetuximab Pre-/Post-Infusion Medication

Premedication for IRRs is allowed at the Investigator's discretion for cetuximab. If used, premedicate with an H1 antagonist (eg, 50 mg of diphenhydramine) IV 30 to 60 minutes prior to the first dose; premedication may be administered for subsequent cetuximab doses based upon clinical judgment and presence/severity of prior IRRs. Post-infusion medications are permitted at the Investigator's discretion.

5.10.3 Prohibited Medications

- Immunosuppressive agents, including disease-modifying anti-rheumatic drugs (eg, anti-tumor necrosis factor [TNF])
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.10.1)
- Any antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, investigational agent, or radiation therapy) is prohibited during the study.

Consideration should be given to withholding antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (eg, alpha blockers for benign prostatic hypertrophy), prior to each dose of NKTR-255, particularly when therapy involves multiple anti-hypertensive drugs and classes other than thiazide diuretics. Antihypertensive medications should be withheld no less than 12 hours and no more than 48 hours prior to each dose of NKTR-255. Antihypertensive medications may be reinstituted in between doses of NKTR-255 if the diastolic pressure exceeds 90 mmHg and/or the systolic pressure exceeds 160 mmHg.

Drugs known to cause QTc interval prolongation must be used with precaution. Refer to https://crediblemeds.org for the list of drugs.

Concomitant use of hematopoietic growth factors such as erythropoietin, granulocyte colony-stimulating factor (filgrastim, pegfilgrastim), granulocytes/macrophage colony-stimulating factor (sargramostim), or thrombopoietin (oprelvekin, eltrombopag) should not be initiated or increased in dose from the start of the Screening period until the completion of the DLT assessment window in the absence of a DLT. After the DLT assessment windows have been completed or after a DLT has been documented, initiation or dose and schedule modifications are allowed in accordance with instructions provided in the package inserts, institutional practice, and/or published guidelines.

Investigators should follow their institutional guidelines for discontinuation of anti-coagulant therapy (eg, aspirin and Plavix [clopidogrel]) before injections. Investigators should understand current best-practice recommendations for pre- and post-procedure management of

antithrombotic therapy, balancing the risk/benefit of modifying antithrombotic therapy in patients.

Live, attenuated vaccines are prohibited within 30 days before the first dose of study drug and while participating in the study. Note: Acceptable vaccines include killed vaccines.

All vaccines against SARS-CoV-2 (including live, attenuated vaccines) are acceptable.


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5.12 Management of Potential Risks Associated with Cetuximab

The most frequently reported adverse reactions in patients receiving cetuximab are provided in the current local prescribing information. Instructions for pre- and post-infusion medication are provided in Section 5.10.2.

To monitor for neutropenia and thrombocytopenia, complete blood cell counts will be done periodically during treatment (Section 1.2). Patients with neutropenia should be monitored for signs of infection. Dose delay may be required to allow recovery of neutrophils or platelets (Section 5.3.2).

To date, no studies evaluating the toxicity of NKTR-255 in combination with cetuximab have been conducted. The toxicity profile of NKTR-255 (systemic inflammation due to expected pharmacology) is not expected to overlap substantially with that of cetuximab (infusion reactions, skin and ocular effects, hypomagnesemia) (Thomas, 2005; Fakih, 2010). However, based on PD studies (Nektar data on file; Chen, 2016), enhancement of cetuximab-mediated

ADCC is possible due to increases in NK cells induced by NKTR-255. While the enhanced ADCC is anticipated to be primarily directed at tumor cells that overexpress EGFR, effects on non-tumor cells expressing lower levels of EGFR may also occur. Therefore, adverse effects of cetuximab may be enhanced and/or encountered when combined with NKTR-255. Clinical manifestations may include rash, erythema, pain, and swelling at the tumor site. Necrosis, pain, ulceration, or bleeding of tumor tissue may occur during and/or after combination therapy.

5.13 Study Assessments

5.13.1 Tumor and Radiographic Assessments

Tumor assessments for all patients will be performed at Screening and every 9 weeks from C1D1 until the patient withdraws consent or starts a new antineoplastic regimen. Tumor response will be evaluated using RECIST 1.1 as the primary (Phase 2) and irRECIST as an exploratory measure. Efficacy assessments are further described in Section 8.0.

5.13.2 Pharmacokinetic Measurements

Blood samples for PK analyses will be collected from all patients (Section 1.2). Serial PK samples will be collected at multiple scheduled sampling times. Concentrations of NKTR-255 and cetuximab will be measured using validated method(s). Concentrations of additional analytes such as total PEG may also be analyzed in plasma samples. Pharmacokinetic parameters such as maximum peak concentration (C_{max}), area under the concentration-time curve (AUC), CL, V, and $t_{1/2}$ will be estimated from plasma concentration-time data where possible.

Blood samples for quantification of NKTR-255 and cetuximab concentrations will be drawn at times listed in the Schedule of Events (Section 1.2) CCI [redacted]. Blood samples for PK analysis will be processed as outlined in the Laboratory Manual. All on-treatment timepoints are intended to align with days on which study drug is administered. If a decision is made to delay dosing after collection of a predose sample, a second predose sample should not be collected. However, all postdose 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. Please refer to the Laboratory Manual for details.


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5.13.5 Electrocardiogram

Electrocardiograms will be performed according to the Schedule of Events (Section 1.2).

Patients must be resting quietly in the supine position for ≥ 5 minutes prior to the specified ECG timepoints. If the ECG assessments coincide close to mealtime, obtain ECG and PK sample prior to meal, if possible.

Interpretation of ECGs and interval duration measurements will be performed locally by the study sites. The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant will be reported as an AE as described in Section 7.1.

See Section 7.15 for monitoring of safety by ECGs.

5.13.6 Serology

Seropositivity for hepatitis B is defined by a positive test for hepatitis B surface antigen (HBsAg) or antibodies to hepatitis B surface and core antigens (anti-HBs and anti-HBc, respectively); hepatitis C (anti-hepatitis C virus [HCV] antibody positive or hepatitis C virus ribonucleic acid [HCV-RNA] quantitation positive).

6.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

6.1 NKTR-255

NKTR-255 will be supplied to the Investigator by Nektar Therapeutics or its designee. Study drug supplies must be kept in an appropriate, secure locked area, and stored in accordance with the conditions specified on the labels.

6.1.1 Drug Description and Formulation

NKTR-255 Drug Product is provided as a sterile, lyophilized powder. CCI [redacted] The vials are preservative free.

6.1.2 Drug Packaging and Labeling

NKTR-255 will be packaged and labeled according to current Good Manufacturing Practices. CCI [redacted]

6.1.3 Drug Reconstitution and Handling

The instructions for reconstitution, dilution, storage, and administration of NKTR-255 Drug Product are described in the Pharmacy Manual.

6.1.4 Drug Storage

NKTR-255 Drug Product should be stored at -CCI [redacted] in its original packaging.

6.1.5 Drug Shipment

Supply of NKTR-255 Drug Product will be shipped at CCI [redacted] to the site pharmacy.

6.2 Cetuximab

Cetuximab will be supplied to the Investigator by Nektar Therapeutics or its designee. With Sponsor approval and, depending on local health authority guidelines and drug availability, cetuximab may be obtained through commercial supply, the site pharmacy, or through a central depository. Information regarding the packaging, labeling, formulation, storage, and handling of commercial cetuximab can be found in the current local prescribing information for cetuximab.

6.3 Study Drug Accountability and Reconciliation

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

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

- Records of product delivery, inventory, temperature monitoring, destruction, and return as per Sponsor's instructions
- Dosages 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

Please refer to the Pharmacy Manual for details.

7.0 ASSESSMENT OF SAFETY OR AES AND SERIOUS AES

7.1 AE Definition and Assessment

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

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

An AE does not include:

- A medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion); an AE is the underlying condition that leads to the procedure
- Pre-existing diseases or conditions present or detected before start of study drug(s) administration which do not worsen or increase in severity or frequency after the administration of study drug(s)
- 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, or other situations where an untoward medical occurrence has not occurred
- Overdose of either study drug(s) or concomitant medication without any signs or symptoms

7.2 Monitoring AEs

All AEs will be assessed by the Investigator and recorded including, but not limited to, the following: the event term, the date of onset and resolution, seriousness, severity, relationship to study drug(s), outcome, treatment of the event, and action taken with the study drug(s). Adverse events will be reported starting immediately after the patient has been administered the first dose of study drug(s) until 60 days after the last dose of study treatment, unless the patient withdraws consent to treat, initiates new anti-cancer therapy, is lost to follow up, or death occurs, whichever comes earlier.

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

Under the latter 2 circumstances, the event will be considered an AE and will be captured as such.

Example 1:

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

Example 2:

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

7.3 Grading of AEs

The severity of an event and the seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of an 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 (Version 5.0) guidelines, CCI [redacted]. If a particular AE is not listed in the NCI-CTCAE, the following criteria will be used:

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

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

7.4 Causality Relationship of AEs

The relationship of each AE to each study drug (NKTR-255 and cetuximab) as applicable will be evaluated by the Investigator using the following definitions:

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

7.5 AE Reporting and Follow-up

All AEs, except for SAEs (Section 7.7) and AEs attributed to protocol-mandated procedures (Section 7.2), will be reported from the time of first study drug(s) administration until 60 days after the last dose of study treatment, unless the patient withdraws consent to treat, initiates new anti-cancer therapy, is lost to follow up, or death occurs. All ongoing AEs will be followed until resolution, the patient is lost to follow-up, patient death, or until 60 days after the last dose of study treatment. In case the AE has not completely resolved up to 60 days after the last dose of study treatment or until a new antineoplastic regimen has been initiated, the final outcome of these ongoing AEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

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

7.6 Serious AE Definition

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

- Results in death.
- Is life-threatening, ie, in the opinion of the Investigator, the 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.

  Note: the following are not considered SAEs:

  - A surgery or procedure that was planned before the patient entered the study and which is part of the planned study procedure
  - Nonmedical reasons, in the absence of an AE

  - A visit to the emergency room or other hospital department for less than 24 hours that does not result in admission (unless considered an important medical or life-threatening event)
- 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 (Section 7.9). An efficacy failure is not considered an SAE. "Life threatening" means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

7.7 Serious AE Reporting

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

All SAEs, regardless of causality attribution, with an onset within 60 days after the last dose of study treatment (EOT), unless the patient withdraws consent to treat, initiates new anti-cancer therapy, is lost to follow up, or death occurs, will be reported to Nektar Therapeutics Drug Safety within **24 hours** after the site becomes aware of the event.

All AEs and SAEs will be recorded in the electronic case report form (eCRF) database within the timelines outlined in the eCRF completion guidelines. At the time of study start, SAEs may be reported using a paper SAE reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system. Nektar or designee will provide training and account information prior to implementing an eSAE system at each site.

7.7.1 Electronic Serious Adverse Event (eSAE) Reporting Process

Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Nektar Drug Safety within 24 hours of the Investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines. If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning,

record the SAE on the paper SAE reporting form and submit within 24 hours of the Investigator's knowledge of the event to Nektar Therapeutics Drug Safety via email or Safety Fax as listed at the beginning of this protocol.

As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines. If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by email or fax when requested and applicable. Transmission of such documents should occur without personal patient identification, maintaining the traceability of a document to the patient identifiers. Additional information may be requested to ensure the timely completion of accurate safety reports. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the patient's eCRF and the event description section of the SAE form.

All SAEs will be followed as described in Section 7.8.

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

7.8 Serious AE Follow-up

All study treatment-related SAEs that have not resolved within 60 days after the last dose of study treatment, until a new antineoplastic regimen has been initiated, loss to follow-up, withdrawal of consent, or death, will be followed until any of the following occurs (whichever comes first):

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

All ongoing SAEs assessed as "unrelated" to study drug(s) will be followed until resolution or until 60 days after the last dose of study treatment or until a new antineoplastic regimen has been initiated. In the case where an unrelated SAE has not completely resolved up to 60 days after the last dose of study treatment or until a new antineoplastic regimen has been initiated, the final

outcome of these ongoing SAEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

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

It is anticipated that during this study a proportion of patients will experience disease progression prior to study discontinuation. Disease progression should not be reported as an AE or SAE. In some patients disease progression may result in clinical manifestations (eg, pleural effusion) that meet "seriousness" criteria (eg, hospitalization). These clinical manifestations may be reported as non-fatal SAEs.

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

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

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

7.10 Pregnancy

7.10.1 Pregnancies in Female Patients

The Sponsor must be notified within 24 hours of the initial report and any follow-up reports of a female study patient becoming pregnant during the course of the study CCI [redacted] via the Pregnancy Notification Form for any pregnancy. The patient, once becoming aware of pregnancy, should reach out to the study Investigator for confirmation and consultation. In order for the Sponsor or designee to collect any pregnancy surveillance information, the pregnant patient will be asked to sign a Pregnancy Follow-up ICF. Pregnancy, although reportable, is not considered an AE/SAE unless a female patient experiences signs or symptoms of pregnancy complications (in which case the AE is the complication, not the pregnancy); however, the contact information for pregnancy reporting is the same as for SAE reporting and listed in Section 7.7 and the List of Study Contacts. Female patients 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 (Section 5.2.3.1, Section 5.2.3.2).

7.10.2 Pregnancies in Female Partners of Male Patients

The Sponsor must be notified within 24 hours of the initial report of a female partner of a male study patient becoming pregnant during the course of the study [redacted] via the Pregnancy Notification Form. A female partner of the male patient will be asked to sign a Pregnancy ICF for follow-up of the pregnancy. The contact information for pregnancy reporting is the same as for SAE reporting and listed in Section 7.7 and the List of Study Contacts. 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 drugs 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.

7.11 Pregnancy Tests

Appendix 7 describes acceptable methods of contraception. Patients must follow these guidelines while on study.

Serum pregnancy tests will be performed on WCBP during Screening, and serum or urine pregnancy test on Day 1 prior to each dose of study drug and at EOT. Serum 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 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.

7.12 Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Events (Section 1.2). Clinical safety laboratory tests (Appendix 4) will be performed by a designated central laboratory. Central laboratory results must be used to determine patient eligibility, unless otherwise stated. In situations where central laboratory results are unavailable for eligibility determination, the Medical Monitor may approve of substitution of local laboratory results (a repeat full set of central laboratory results must be obtained prior to dosing). Clinical laboratory test data will be reviewed by the Investigator or Sub-Investigator. Additional clinical laboratory tests may be ordered at the Investigator's or qualified Sub-Investigator's discretion.

For treatment decisions at Cycle 2 and beyond, blood draw for the central laboratory may be obtained up to 5 days prior to the scheduled day of treatment. Depending on the turn-around time for the central laboratory, the results of these safety laboratory tests may not be available prior to the scheduled treatment. If the results are not available, or, at the discretion of the Investigator,

local laboratory results may be used to determine eligibility for retreatment. In all cases, if local laboratory results are used for retreatment decisions, duplicate central laboratory tests must be submitted to the central laboratory.

Treatment decisions require results for the following tests: hemoglobin, absolute neutrophil count (ANC), platelets, bicarbonate/carbon dioxide (CO_2), calcium, chloride, potassium, sodium, and serum creatinine.

The Investigator or designee will review all laboratory results for clinical significance. Any laboratory result deemed clinically significant (ie, associated with signs and symptoms, requires treatment, or requires follow-up) will be recorded as an AE as described in Section 7.1.

7.13 Physical Examinations

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

7.14 Vital Signs

Vital sign measurement will be recorded according to the Schedule of Events (Section 1.2). Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation (oxygen saturation at Screening and on dosing days only), and temperature (oral). It is preferred that the same arm be used for all blood pressure readings, if possible. Where feasible, vital signs should be measured before having blood drawn for laboratory evaluations.

The study site must be equipped for medical emergencies and have access to an intensive care unit.

If the patient experiences a Grade > 2 IRR or hypotension on the dosing day, the patient may be monitored overnight at the discretion of the Investigator. Longer periods of monitoring may be implemented at the discretion of the Investigator.

7.15 Electrocardiograms

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

7.16 Cardiac Function

An echocardiogram, nuclear scan, or multigated acquisition (MUGA) scan will be performed for all patients as per schedule of assesments, within 60 days prior to dosing and at EOT to assess cardiac function and left ventricular ejection fraction (LVEF). The same assessment method should be used for the same patient throughout the study, if feasible.

8.0 ASSESSMENT OF EFFICACY

8.1 Treatment Response Assessment

Tumor response will be evaluated using RECIST 1.1 criteria (Eisenhauer, 2009; Appendix 2). Tumor burden will be characterized prior to enrollment, and response assessments will be performed approximately every 9 weeks starting from C1D1.

8.2 Tumor Imaging (Computed Tomography or Magnetic Resonance Imaging)

Computed tomography (CT) with contrast or magnetic resonance imaging (MRI) (for patients who cannot tolerate CT contrast) will be obtained to document metastatic disease, identify target lesions as described in RECIST 1.1, and to assess response and disease progression. Imaging by CT scan with contrast or MRI will be performed at Screening, and approximately every 9 weeks during the treatment period regardless of cycle number or dose interruption.

Scans taken as part of standard medical practice up to 42 days prior to first dose of study treatment can be used for Screening. During the treatment, scans may be performed at timepoints other than every 9 weeks as clinically indicated to assess tumor progression. A standard-of-care brain MRI occurring prior to the 28-day screening window may be acceptable based on consultation with the Medical Monitor.

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At Screening, a brain MRI is only required for patients with a history of brain metastases and should be followed as clinically indicated. Other scans may be included as clinically indicated.

For patients who stop study treatment in the absence of disease progression (eg, due to unexpected toxicity), scans should continue to be collected approximately every 9 weeks until disease progression or initiation of systemic anti-tumor therapy other than the study treatment (whichever is earlier) or unless patient withdraws consent.

The same imaging procedure and specifications (eg, contrast agent, scanner, slice thickness, etc.) used to define measurable target and non-target lesions must be used throughout the study for each patient.

Computed tomography scans may not be performed at sites or in countries where additional radiology approval is required, unless that approval is sought and granted.

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

9.1 General Considerations

In general, continuous data will be summarized by descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of patients.

A description of analysis methods and detailed definitions for efficacy and safety endpoints 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.

9.2 Determination of Sample Size

This is a Phase 1b/2 dose escalation and dose expansion study. During dose escalation (Phase 1b), successive groups of at least 3 patients will be treated at each dose level until the MTD and/or RP2D is determined. Additional patients may be added to each dose level based on the scheme and rules outlined in Section 5.2.3.4 or Sponsor determination of the need for additional data to further evaluate the benefit/risk profile. It is estimated that approximately 30 patients will be enrolled in the dose escalation.

A Bayesian design will be used CCI [redacted].

For HNSCC and CRC cohorts, an initial 12 patients will be enrolled into stage 1 of Cohorts A and B, respectively, and the enrollment will continue to a maximum of 24 patients or until the criteria of Pr(ORR > 0.25 | Data) > 30% is met. Patient enrollment to Cohorts A1 and B1 will be gated by the Bayesian criteria. After the initial 5 patients' first tumor assessment, subsequent patients will be randomized to the second stage of Cohort A versus Cohort A1, and the second stage of Cohort B versus Cohort B1 using adaptive randomization.

With adaptive randomization, patients will be adaptively assigned proportional to weighted clinical utility function based on available response data. Higher scores are assigned to better responses: [CR ≥ 6m = 6], [CR = 5], [PR ≥ 6m = 4], [PR = 3], [stable disease (SD) ≥ 6m = 2], [SD = 1], [progressive disease = 0], thus a new patient will have higher chance to be assigned to the cohort with better responses. A minimum of 0.1 allocation probability will be retained for each cohort. A maximum of 50 patients each will be enrolled into Cohort A and Cohort B, and a maximum of 26 patients each will be enrolled into Cohort A1 and Cohort B1.

Prior for ORR is set to be Beta(0.25,0.75) corresponding to a prior belief of ORR = 0.25 with 1 effective sample. The following Bayesian decision rules will be applied to Cohort A, Cohort A1, Cohort B, and Cohort B1, respectively, to guide the Go/No-Go decision:

- Select an arm as superior if

- Pr(ORR > 0.25 | Data) > 80% and Pr(ORR > 0.10 | Data) > 90%
- Suspend accrual to an arm if Pr(ORR ≤ 0.10 | Data) > 85%
- Achieve maximum sample size

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With adaptive randomization, patients will be adaptively assigned proportional to weighted clinical utility function based on available response data. Higher scores are assigned to better responses: [CR ≥ 6m = 6], [CR = 5], [PR ≥ 6m = 4], [PR = 3], [SD ≥ 6m = 2], [SD = 1], [progressive disease = 0], thus a new patient will have higher chance to be assigned to the cohort with better responses. A minimum of 0.1 allocation probability will be retained for each cohort.

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Prior for ORR is set to be Beta(0.25, 0.75) corresponding to a prior belief of ORR = 0.25 with 1 effective sample. The following Bayesian decision rules will be applied to Cohort C, Cohort C1, Cohort D, Cohort D1, Cohort E, and Cohort E1, respectively, to guide the Go/No-Go decision:

- Select an arm as superior if
  - Pr(ORR > 0.25 | Data) > 80% and Pr(ORR > 0.10 | Data) > 90%
- Suspend accrual to an arm if Pr(ORR ≤ 0.10 | Data) > 85%
- Achieve maximum sample size

9.3 Safety Stopping Rules

A Bayesian sequential monitoring design (Thall, 1995) will be employed to monitor safety of all patients enrolled in the study after 6 patients have been treated. See Section 5.5.4 for details.

9.4 Interim Analyses

No interim analyses are planned for this study.

9.5 Analysis Sets

Safety Population: All patients who receive at least 1 dose (or partial dose) of NKTR-255

Cetuximab-only Population: All patients who receive at least 1 dose (or partial dose) of cetuximab but without any dose of NKTR-255

DLT Population: All patients who receive at least 1 dose of the combination treatment of NKTR-255 and cetuximab and who complete the DLT observation period or discontinue from the study treatment due to a DLT will be included, where DLT window is 21 days since the first dose of NKTR-255.

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

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CCI [redacted]

Response-evaluable Population: The Response-evaluable Population is defined as patients who have measurable disease (per RECIST 1.1) at baseline, receive at least 1 dose (or partial dose) of study drug, and have at least 1 post-baseline assessment of tumor response.

9.6 Planned Analyses

9.6.1 Safety

Safety assessments will include Safety Population with treatment-emergent AEs with categorization of treatment related with incidences of serious and severe (≥ Grade 3) AEs, clinical laboratory tests including cardiac function tests, vital signs, physical examinations, and ECGs.

Adverse events and toxicity severity will be evaluated according to NCI-CTCAE Version 5.0 toxicity grading system. Safety assessments will be performed by medical review of AEs, vital signs, and laboratory results.

The incidence rate of DLTs will be evaluated by dose level for the DLT Population. Treatment-emergent AEs will be summarized by preferred term, system organ class, NCI-CTCAE grade of severity, and relationship to the study treatment by dose level for Phase 1b (Dose Escalation), CCI [redacted] for the Safety Population. All TEAEs will be summarized by incidence, severity, and relationship to study drug(s).

A TEAE is defined as (regardless of intensity), any AE that occurs after initiation of study treatment on C1D1 until 60 days (inclusive) after the last dose of study treatment. Adverse events with a starting date after the start of new anti-cancer therapy are not considered TEAEs.

Vital signs (including change in weight) and clinical laboratory test results will be summarized descriptively by dose level in Phase 1b (Dose Escalation) CCI [redacted] for the Safety Population. A listing and summary of patients who discontinued study drug(s) due to an AE will be provided.

A data listing for deaths will be provided.

9.6.2 Demographics and Baseline Characteristics

Demographic data (age, sex, ethnicity, body weight) and baseline disease characteristics will be summarized and presented in data listings for the Phase 1b (Dose Escalation) and Phase 2 (Dose Expansion) portions separately for each disease type.

9.6.3 Efficacy

The primary efficacy measurement will be ORR by RECIST 1.1. Other efficacy outcomes will include:

- BOR
- DOR
- CBR
- TTR
- PFS
- OS
- ORR by irRECIST

Objective response rate, BOR, DOR, CBR, TTR, PFS, and OS efficacy endpoints will be assessed in the Response-evaluable Population, where DOR and TTR will be analyzed among responders. In addition, OS will be presented for the Safety Population.

Objective response rate, CBR, and each BOR category will be calculated along with the 95% confidence intervals (CIs) based on the exact method. The Kaplan-Meier method will be used for the analyses of PFS, OS, and DOR. Summary statistics will be provided for time since C1D1 to first response among responders.

Final statistical considerations and analyses will be detailed in the SAP.

9.7 Concomitant Medications

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

9.8 Missing Data

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

10.0 STUDY OR STUDY SITE TERMINATION

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

- Study is terminated due to safety concerns (ie, the benefit-risk balance is unacceptable)
- Lack of efficacy or not meeting the study objectives
- Development of NKTR-255 is terminated

If an Investigator suspends or terminates their study site, the Investigator will promptly (if possible, within 24 hours) inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports, summaries, and other documentation as required by health authorities, IRB/IEC, and other regulatory requirements.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

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

11.1 Changes to the Protocol

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/IEC and the regulatory agency, as required by regulations, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve only logistical or administrative aspects of the study. Any deviation may result in the patient having to be withdrawn from the study and rendering that patient nonevaluable.

All protocol deviations and the reasons for such deviations are to be documented and reported to the Sponsor promptly.

11.2 Monitoring

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

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

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

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

12.0 ETHICAL CONSIDERATIONS

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

12.1 IRB/IEC Approval

Before enrollment of patients into the study, as required by FDA regulations (21 CFR § 56), ICH GCP, regulatory authority requirements, and local regulations, the current protocol, Investigator's Brochure, and ICF will be reviewed and approved by the applicable regulatory authority and/or competent IRB/IEC. A letter documenting the IRB/IEC approval must be received by the Sponsor before the initiation of the study at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol in accordance with Section 11.1.

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

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

12.2 Written Informed Consent

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

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

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

surveillance information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form (see Section 7.10).

13.0 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection Instruments and Source Documents

13.1.1 Study Records

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

13.1.2 Data Collection Instruments

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

13.2 Retention of Essential Documents

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

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

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

13.3 Confidentiality

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

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

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

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

13.4 Security Measures

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

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

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APPENDIX 1: PRIOR CALIBRATION AND ON-STUDY DOSE ESCALATION RECOMMENDATIONS OF THE BAYESIAN LOGISTIC REGRESSION MODEL

1. INTRODUCTION

An adaptive Bayesian Logistic Regression Model (BLRM) for dose escalation with overdose control (EWOC) similar to that proposed by Babb et al. (1998) will be used to guide dose escalation in this study.

As indicated in the Protocol Section 5.8, "the dose recommended by the adaptive Bayesian logistic model will be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of the analysis in determining the next dose level to be investigated. Generally, the study will not treat patients at a dose higher than the model-recommended dose. However, the study may escalate to or stay at a dose higher than the model-recommended dose if such a decision is consistent with accepted clinical practice (eg, standard 3+3 escalation rules serving as guidance). The dose given to the next dose group in the study will be based on considerations of the MTDs estimated by the BLRM, and on an overall clinical assessment of all available safety, tolerability, PK, and PD data from all cycles at all different dose levels tested."

The purpose of this document is to describe the statistical details of the BLRM for dose escalation with EWOC and decision criteria. The performance metrics (operating characteristics) that illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships through computer simulation are also presented. In addition, recommendations of the next dose level by BLRM with overdose control principle are also provided under various hypothetical outcome scenarios in early groups to show how it facilitates on-study dose-escalation decisions.

2. STATISTICAL DETAILS OF BAYESIAN LOGISTIC REGRESSION MODEL

2.1. Statistical Model

The dose-toxicity relationship in the dose escalation part of the study is described by the following model:

$$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*),\ \alpha > 0,\ \beta > 0$$

where $\text{logit}(\pi(d)) = \ln(\pi(d)/(1-\pi(d)))$, $\pi(d)$ is the probability of a DLT at dose d.

Doses are rescaled as d/d* with reference dose d*=6μg/kg. As a consequence, α is equal to the odds of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

2.3 Prior Specification

A vague bivariate normal prior for the model parameters (log(α), log(β)) is elicited based on prior guesses (medians) from preclinical data and wide confidence intervals. The parameters of the prior distributions of model parameters and the assigned weights are provided in Table 1. Figure 1 illustrates the resulting prior distribution of DLT rate derived from the prior given in Table 1.

Table 1. Prior Parameters for Bivariate Normal Distribution of Model Parameters

Parameters	Mean	Standard deviation	Correlation
log(α), log(β)	(0, -0.017)	(2.841, 0.515)	0

- The approximate effective sample size (ESS) of the prior is between 0.9 and 1 for all doses considered. For prior DLT rate π, and approximation of ESS can be obtained by moment-matching of prior mean (m) and standard deviation (s) to that of a beta distribution with parameters (a, b), so that:

  $ESS = a + b = m(1-m) / s^2 - 1$

2.4. Toxicity Intervals and EWOC Criteria

Dose recommendation will be based on posterior summaries for each dose, primarily the posterior probabilities for the following three toxicity intervals:

1. [0,16%) under-dosing

2. [16%,33%) targeted toxicity

3. [33%,100%] excessive toxicity

The EWOC criteria for a dose level d µg/kg is specified as Prob(DLT rate ≥ 33% | data) < 25%, ie, the posterior probability that the dose level d µg/kg is excessively toxic (with a DLT rate of 33% or higher) must be low (less than 25%).

2.5. Dose Escalation Procedures and Decision Criteria

After each group of patients has passed their DLT observation window, the posterior distribution for the model parameters will be obtained. Based on the posterior distribution of all model parameters, the corresponding posterior distributions for the probabilities of DLT at different dose levels are obtained.

The recommended dose is the one with the highest posterior probability of the DLT rate falling in the target toxicity interval [16%, 33%) among the doses fulfilling EWOC, ie, it is unlikely (< 25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval. Note that the dose that maximizes the posterior probability of targeted toxicity is the best estimate of the MTD, but it may not be an admissible dose according to the overdose criterion if the amount of data is insufficient. If vague prior information is used for the probabilities of DLT, in the early stages of the study this escalation procedure will reflect a conservative strategy.

The MTD will be declared when the posterior probability of targeted toxicity is at least 60% for a dose and at least 6 patients are treated at that dose. An RP2D may be identified without identification of MTD. CCI

3. OPERATING CHARACTERISTICS FROM SIMULATION

This section presents the operating characteristics that illustrate the precision of the design in estimating the MTD under various assumed true dose-toxicity relationships.

3.2. Decision Rules

Each group consisted of 3 patients. Dose escalation followed the following rule:

- escalate to the dose which maximizes the probability of the targeted toxicity region and satisfies the overdose criteria if it is a ≤ m% increase from the current dose
- if the recommended dose satisfying the overdose criteria is a > m% increase in dose, then escalate to the highest dose level which is a ≤ m% increase from the current dose

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Intermediate dose levels have been added so that the above can be implemented in by restricting dose increments to a maximum of 2 dose levels among the doses described previously.

The MTD stopping rule is that at least 6 patients have been evaluated at a dose level for which the posterior probability of targeted toxicity is at least 60%. All simulations were conducted under the assumption of a maximum sample size of 30.

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The protocol also states that the study may escalate or stay at a dose higher than the model-recommended dose if such a decision is consistent with accepted clinical practice (eg, standard 3+3 escalation rules serving as guidance). CCI

However, there may be other less likely situations not being accounted for in the simulations.

In addition, the study will include a sentinel patient who will be treated at the introduction of each dose (and if no patients have been treated at higher doses) before treating more patients. This requirement has also not been accounted for in the simulations.

3.3. Dose Chosen if MTD Stopping Criteria Are Not Achieved

In the simulation study, when MTD cannot be identified within 30 patients using the above outlined BLRM methodology, dose chosen for summary of operating characteristics is the highest dose which meets all of the following criteria:

1. Selected dose satisfies EWOC
2. Selected dose is less than or equal to the last dose that was tested
3. There are at least 3 patients treated at that dose

4. Selected dose must be less than or equal to highest dose at which observed proportion of DLTs is 33% or less (upper limit of targeted toxicity interval)

3.4. Assumed True Dose-toxicity Relationships

Simulations are performed for the BLRM under a total of 5 scenarios of true dose-DLT relationship (Figure 2; Table 2):

a. Dose-DLT relationship is a steep curve and MTD is reached at middle dose level

b. Dose-DLT relationship is a steep curve and MTD is reached at early dose level

c. Dose-DLT relationship is a flat curve and MTD is reached at middle dose level

d. Dose-DLT relationship is a flat curve and MTD is reached at late dose level

e. Dose-DLT relationship is a steep curve and MTD is reached at late dose level

3.5. Simulation Results

Operating characteristics are reviewed to investigate overall performance of the BLRM under each true scenario.

4. HYPOTHETICAL DOSE ESCALATION SCENARIOS IN EARLY GROUPS

Aside from the overall operating characteristics studied above, the design should make reasonable decisions during a study based on the observed toxicities. After completion of a given group, the decision to dose escalate and actual dose chosen for the subsequent group will depend on the recommendation of the BLRM per EWOC principle and medical review of available clinical, PK/PD, and laboratory data.


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5. DISCUSSION

The Bayesian Logistic Regression Model for the dose-escalation enables us to incorporate the preclinical information, as well as to update the recommended dose based on all safety data in the study.

On-study recommendations based on the model are consistent with the clinical decision-making process and should be considered in conjunction with other available clinical information by the Nektar Clinical Trial Team and study Investigators in deciding the dose levels to be tested in order to determine the MTD/RP2D.

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APPENDIX 2: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST 1.1)

Response Assessment	RECIST Guideline, Version 1.1
Target Lesions	
CR	Disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤ 10 mm
PR	≥ 30% decrease in the sum of the longest diameter of the target lesions compared with baseline
PD	≥ 20% increase of at least 5 mm in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded **OR** The appearance of new lesions, including those detected by FDG-PET
SD	Neither PR nor PD
Non-target Lesions	
CR	Disappearance of all non-target lesions and normalization of tumor marker levels
SD	Persistence of 1 or more non-target lesions and/or the maintenance of tumor marker levels above normal limits
PD	The appearance of 1 or more new lesions or unequivocal progression If patient has measurable disease, an increase in the overall level or substantial worsening in non-target lesions, such that tumor burden has increased, even if there is SD or PR in target lesions If no measurable disease, an increase in the overall tumor burden comparable in magnitude with the increase that would be required to declare PD in measurable disease (eg, an increase in pleural effusions from trace to large, or an increase in lymphangitic disease from localized to widespread)

CR = complete response; FDG-PET = fluorodeoxyglucose (FDG)-positron emission tomography; PD = progressive disease; PR = partial response; SD = stable disease

Reproduced from Eisenhauer, 2009.


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APPENDIX 4: CLINICAL LABORATORY TESTS (ONLY TESTS DONE VIA CENTRAL LABORATORY)

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Chemistry</th><th>Serology</th></tr>
<tr><td rowspan="8">• Hemoglobin (Hgb)
• Hematocrit (HCT)
• Red blood cell (RBC) count
• Platelet count
• White blood cell (WBC) count
• Neutrophils
• Lymphocytes
• Monocytes
• Eosinophils
• Basophils
• Mean corpuscular volume (MCV)
• Mean corpuscular hemoglobin (MCH)
• Mean corpuscular hemoglobin concentration (MCHC)</td><td rowspan="8">• AST (SGOT)
• ALT (SGPT)
• Alkaline phosphatase (ALP)
• Albumin
• Creatinine
• Calculated creatinine clearance
• Calcium
• Ferritin
• Gamma-glutamyl transferase (GGT)
• Glucose
• Total protein (TP)
• Total and direct bilirubin
• Sodium
• Potassium
• Chloride
• Magnesium
• Carbon dioxide (CO_2) content or bicarbonate
• Blood urea nitrogen (BUN)
• Lactate dehydrogenase (LDH)
• Uric acid</td><td>• Hepatitis B surface antigen (HBsAg)
• Hepatitis B core antigens (anti-HBc)
• Hep B DNA
• Hepatitis C virus antibody (anti-HCV)
• Hepatitis C virus ribonucleic acid (HCV-RNA)
• Human immunodeficiency virus (HIV) antibody</td></tr>
<tr><td>Additional Labs</td></tr>
<tr><td>• Creatine kinase (CK)
• Thyroid-stimulating hormone (TSH)
• Free thyroxine (free T4)
• Free or total triiodothyronine (T3)[a]
• Lipase
• Amylase</td></tr>
<tr><td>Coagulation</td></tr>
<tr><td>• Partial thromboplastin time (PTT)
• Prothrombin time (PT)
• International normalized ratio (INR)</td></tr>
<tr><th colspan="3">Urinalysis</th></tr>
<tr><td colspan="2">• Specific gravity
• pH
• Glucose
• Protein
• Bilirubin
• Ketones
• Leukocyte esterase
• Blood</td><td>For positive protein, white blood cell or blood, a microscopic examination including:
• Red blood cells
• White blood cells
• Epithelial cells
• Bacteria
• Crystals
• Casts</td></tr>
<tr><td colspan="3">Minimal acceptable laboratory safety tests for local laboratory to assess suitability for retreatment of NKTR-255</td></tr>
<tr><th colspan="2">Hematology</th><th>Chemistry</th></tr>
<tr><td colspan="2">• Hemoglobin
• Platelet count
• Neutrophils including bands (absolute)</td><td>• Creatinine
• Sodium
• Potassium
• Chloride
• Calcium
• Bicarbonate/CO_2</td></tr>
</table>

a. T3 should be tested in case of an abnormal TSH and normal T4. See the Laboratory Manual for further information.

APPENDIX 5: ECOG PERFORMANCE SCALE

ECOG Grade	ECOG Status
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, eg, 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

ECOG = Eastern Cooperative Oncology Group

Source: Oken, 1982.

APPENDIX 6: CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) CREATININE EQUATION

$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] x
1.159 [if Black]

where:

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2

S_{Cr} (standardized serum creatinine) = mg/dL

$\kappa = 0.7$ (females) or 0.9 (males)

$\alpha = -0.329$ (females) or -0.411 (males)

min = indicates the minimum of S_{Cr}/κ or 1

max = indicates the maximum of S_{Cr}/κ or 1

age = years

Source: Levey, 2009.

APPENDIX 7: ACCEPTABLE METHODS OF CONTRACEPTION

Highly Effective Methods of Contraception	Progestogen-only hormonal contraception associated with inhibition of ovulation
	Hormonal methods of contraception including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, implants, transdermal and intrauterine hormone-releasing system (IUS)
	Bilateral tubal ligation
	Vasectomized partner
	Intrauterine devices (IUD)
	Complete abstinence
	Local laws and regulations may require use of alternative and/or additional contraception methods
Additional Method for Male Patients	Condom
	NOTE: Partners of male patients are to use one highly effective method of contraception
Unacceptable Methods for Contraception	Vaginal sponge with spermicide
	Progestin only pills
	Cervical cap with spermicide
	Diaphragm with spermicide
	Periodic abstinence (calendar, symptothermal, post-ovulation methods)
	Withdrawal (coitus interruptus)
	Spermicide only
	Lactation amenorrhea method (LAM)
	Male condoms with or without spermicide for partners of female patients, as the only method of contraception
	Female condoms
	A male and a female condom used together