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CLINICAL PROTOCOL

Protocol Number:	20-214-36
Title:	A Phase 2/3, Randomized, Open-label Study to Compare Bempegaldesleukin Combined with Pembrolizumab Versus Pembrolizumab Alone in First-Line Treatment of Patients with Metastatic or Recurrent Head and Neck Squamous-Cell Carcinoma with PD-L1 Expressing Tumors (PROPEL-36)
Version:	Original
Date:	14 June 2021
US IND No.:	153938
Ex US:	Non-IND
EudraCT No.:	2021-002461-18
Investigational Products:	bempegaldesleukin (NKTR-214) in combination with pembrolizumab
Indication:	Recurrent or metastatic head and neck squamous cell carcinoma
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA
Study Medical Monitor:	[redacted]

PRINCIPAL INVESTIGATOR COMMITMENT

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

_____ _____

Principal Investigator Signature **Date**

Printed Name: _____

Institution: _____

Address _____

PROTOCOL APPROVAL PAGE

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DocuSigned by:
[redacted]
Signing Reason: I approve this document
Signing Time: Jun-17-2021 | 9:14:22 AM PDT
902C500B4C584D598935883E01E93872

Signature

Printed Name: [redacted]

Position: [redacted]

LIST OF STUDY CONTACTS

Study Contact	Name	Contact Information
Medical Monitor	[redacted]	[redacted]
Nektar Medical Monitor	[redacted]	[redacted]
Serious AEs, AEs of Special Interest, Events of Clinical Interest, and Pregnancy Reporting	[redacted]	[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ACRONYMS AND ABBREVIATIONS

Abbreviation or Term	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT (SGPT)	alanine transaminase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate transaminase (serum glutamic oxaloacetic transaminase)
bempeg, BEMPEG	abbreviation for bempegaldesleukin, the International Nonproprietary Name (INN) for NKTR-214
bempegaldesleukin	International Nonproprietary Name (INN) for NKTR-214
BICR	blinded independent central review
BTLA	B- and T-lymphocyte attenuator
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran Mantel Haenszel
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CPS	combined positive score
CR	complete response
CRF	case report form
CRR	complete response rate
CRS	cytokine-release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTLA-4	cytotoxic T lymphocyte-associated protein 4
CVA	cerebrovascular accident
DCI	data collection instrument
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid

Abbreviation or Term	Definition
DOAC	direct oral anticoagulant
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECLA	electrochemiluminescence assays
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOI	end of infusion
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQol-5D
EQ-5D-5L	5-level EuroQol-5D
eSAE	electronic serious adverse event
FA	final analysis
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEP	gene expression profile
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	head and neck squamous-cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
HRQoL	health-related quality of life
IA1	first interim analysis (Interim Analysis 1)
IA2	second interim analysis (Interim Analysis 2)

Abbreviation or Term	Definition
ICF	informed consent form
ICH	International Council for Harmonisation
ICOS	inducible T-cell co-stimulator
IEC	independent ethics committee
IFN-γ	interferon-γ
IHC	immunohistochemistry
IL-2	interleukin-2
IL-2Rαβγ	interleukin-2 receptor alpha beta gamma
IL-2Rβγ	interleukin-2 receptor beta gamma
imAE	immune-mediated adverse event (also referred to as immune-related AEs [irAEs] in this document)
IMG	immunogenicity
IND	Investigational New Drug application
INN	International Nonproprietary Name
INR	international normalized ratio
irAE	immune-related adverse event (also referred to as immune-mediated AEs [imAEs] in this document)
IRB	institutional review board
IRT	Interactive Response Technology
ITT	intent-to-treat
IV	intravenous
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
LVEF	left ventricular ejection fraction
mg	milligram
min	minute(s)
mL	milliliter
MRI	magnetic resonance imaging
msec	millisecond
MTD	maximum tolerated dose
MUGA	multigated acquisition

Abbreviation or Term	Definition
NCI	National Cancer Institute
NK	natural killer
NKTR-214	bempegaldesleukin (International Nonproprietary Name)
NSAE	nonserious adverse event
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PEG	polyethylene glycol
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
q2w	every 2 weeks
q3w	every 3 weeks
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-H&N35	Quality of Life Questionnaire head and neck cancer specific module
QTcF	Fridericia's corrected QT interval
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-2	recombinant human interleukin-2
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
rtPA	recombinant tissue plasminogen activator
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

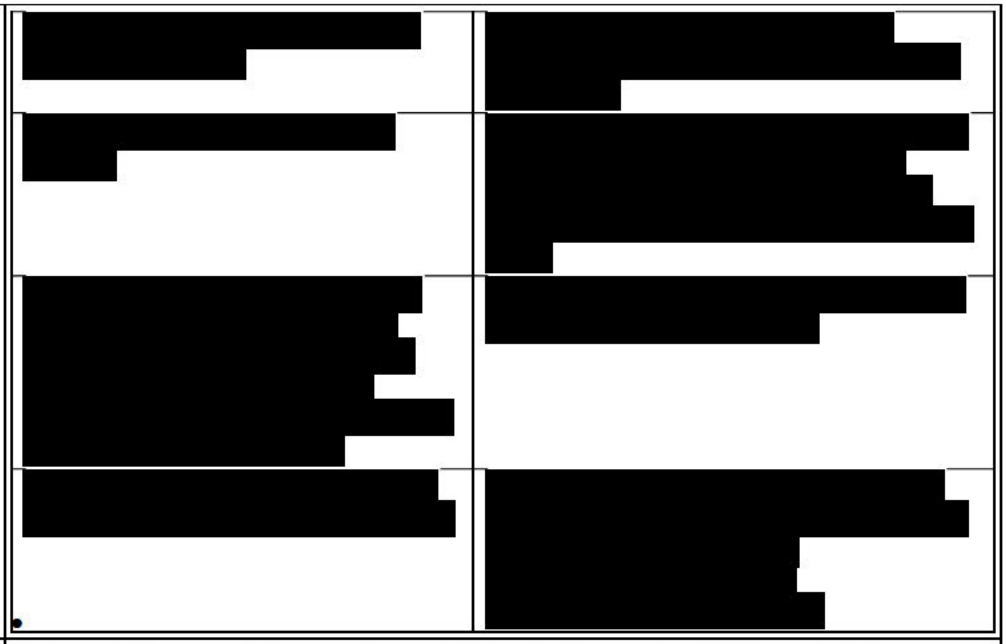
Abbreviation or Term	Definition
SJS	Stevens-Johnson Syndrome
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TIA	transient ischemic attack
TIL	tumor infiltrating lymphocyte
TME	tumor microenvironment
TNBC	triple-negative breast cancer
Treg	regulatory T cell
TTR	time to response
ULN	upper limit of normal
US, USA	United States (of America)
VAS	visual analog scale
WBC	white blood cell
WOCBP	women of childbearing potential

1.0 STUDY SYNOPSIS

<table>
<tr><td>Title of Study:</td><td>A Phase 2/3, Randomized, Open-label Study to Compare Bempegaldesleukin Combined with Pembrolizumab Versus Pembrolizumab Alone in First-Line Treatment of Patients with Metastatic or Recurrent Head and Neck Squamous-Cell Carcinoma with PD-L1 Expressing Tumors (PROPEL-36)</td></tr>
<tr><td>Sponsor:</td><td>Nektar Therapeutics</td></tr>
<tr><td>Name of Finished Product(s):</td><td>Bempegaldesleukin (NKTR-214 drug product)
Keytruda®</td></tr>
<tr><td>Name of Active Ingredient(s):</td><td>Bempegaldesleukin (NKTR-214) drug substance
Pembrolizumab (anti-programmed cell death protein 1 [anti-PD-1] antibody)</td></tr>
<tr><td>Phase of Development:</td><td>Phase 2/3</td></tr>
<tr><td>Objectives and Endpoints:</td><td>In patients who are aged 18 years and older with recurrent or metastatic head and neck squamous-cell carcinoma (HNSCC) and positive programmed cell death ligand 1 (PD-L1) expression (defined by combined positive score [CPS] ≥ 1) who have not received prior therapy for the treatment of recurrent or metastatic HNSCC, the primary objectives and endpoints are:
<table>
<tr><th>Primary Objective</th><th>Endpoint</th></tr>
<tr><td>To compare the overall survival (OS) of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy.</td><td>OS, defined as the time from randomization to death due to any cause.</td></tr>
<tr><td>To compare the objective response rate (ORR) of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy.</td><td>ORR, defined as the rate of confirmed complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by blinded independent central review (BICR).</td></tr>
</table>
The secondary objectives and endpoints listed below involve comparison of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy in first-line patients with recurrent or metastatic HNSCC and positive PD-L1 expression (defined by CPS ≥ 1) who have not received prior therapy for the treatment of recurrent or metastatic HNSCC:
<table>
<tr><th>Secondary Objective</th><th>Endpoint</th></tr>
<tr><td>To compare progression-free survival (PFS).</td><td>PFS, defined as the time from randomization to the first documented disease progression (per RECIST 1.1 by BICR) or death due to any cause, whichever occurs first.</td></tr>
</table></td></tr>
</table>

To compare time to deterioration in global health status/quality of life, pain, and swallowing.	The time from baseline to a ≥ 10-point decrease from baseline with confirmation by the subsequent visit of a ≥ 10-point deterioration from baseline in: • Global health status/quality of life assessment based on the global health status/quality of life scales of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30). • Pain based on the pain multi-item scales of EORTC QLQ head and neck cancer specific module (EORTC QLQ-H&N35). • Swallowing based on the swallowing multi-item scales of EORTC QLQ-H&N35.
To compare mean change from baseline in global health status/quality of life.	Mean change from baseline in global health status/quality of life scales of EORTC QLQ-C30.
To compare the overall safety and tolerability.	Safety will be based on assessments of treatment-emergent adverse events (AEs) and serious AEs (SAEs).

[redacted]

	
Duration of Treatment:	Patients will be treated for a maximum of 35 cycles (approximately 2 years) of therapy following the date of the first dose of study drug or until disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator decision to discontinue treatment, patient decision to discontinue treatment or withdraw consent, loss to follow-up, or Sponsor decision to terminate the trial, whichever occurs first. Treatment may continue beyond progression if there is clinical benefit as determined by the Investigator. Patients who stop study drug after receiving 35 cycles (approximately 2 years) of study drug for reasons other than disease progression or intolerability, or patients who attain a complete response and stop study drug may be eligible for up to 17 cycles (approximately 1 year) of retreatment upon experiencing Investigator-determined radiographic disease progression.
Study Population:	Patients aged 18 years and older with recurrent or metastatic HNSCC and positive PD-L1 expression (defined by CPS $\geq$ 1) who have not received prior therapy for the treatment of recurrent or metastatic HNSCC.
Number of Patients (Planned):	Approximately 500 patients (250 per arm).
Number of Study Sites:	Approximately 225 sites.
Countries:	Approximately 35 countries.
Study Design:	This is a multicenter, randomized, open-label, Phase 2/3 study that will evaluate the efficacy and safety of bempegaldesleukin combined with pembrolizumab compared with pembrolizumab monotherapy in patients with recurrent or metastatic HNSCC with positive PD-L1 expression (CPS $\geq$ 1). The study will use an adaptive design based on prespecified criteria and an independent, external Data Monitoring Committee (DMC) to monitor efficacy and safety. Safety will be evaluated by the DMC approximately twice a year. The first interim analysis will address futility. Enrollment will pause for approximately 4 months after approximately 200 patients have been randomized, and the first interim analysis will occur at least one month after the last patient of the Phase 2 portion has been randomized into the study. If the ORR passes the prespecified futility boundary, the Phase 3 portion of the study will begin with an expected 300 additional patients to be randomized. The second interim analysis will be conducted when approximately 500 patients have been randomized and about 231 overall

	survival events have been observed. At the second interim analysis, if the OS efficacy boundary is crossed, the trial will be stopped for efficacy. Otherwise, conditional power will be calculated to determine the overall survival event size for final analysis. Patients will be randomized at a 1:1 ratio to receive one of two treatments: • Arm A: Bempegaldesleukin plus pembrolizumab every 3 weeks (q3w) for up to 35 cycles (approximately 2 years). • Arm B: Pembrolizumab monotherapy q3w for up to 35 cycles (approximately 2 years). Randomization will be stratified according to the following factors: 1. Disease status (metastatic vs recurrent only). 2. PD-L1 tumor expression determined by PD-L1 immunohistochemistry (IHC) 22C3 PharmDx (CPS ≥ 20 vs CPS 1-19) at either a local or the central laboratory. Note: CPS is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen should be considered to have PD-L1 expression if CPS ≥ 1. 3. Human papillomavirus (HPV) status for oropharyngeal cancer determined by p16 IHC (positive vs negative). For patients with cancers of the oral cavity, hypopharynx, and larynx, HPV status is considered HPV negative. Patients who attain a complete response may consider stopping study drug if they meet criteria for holding therapy. Patients who stop study drug after receiving 35 cycles (approximately 2 years) of study drug for reasons other than disease progression or intolerability, or patients who attain a complete response and stop study drug may be eligible for up to 17 cycles (approximately 1 year) of retreatment upon experiencing Investigator-determined radiographic disease progression. The decision to retreat will be at the discretion of the Investigator only if the patient meets the criteria for retreatment and the trial is ongoing. After the end of treatment, each patient will be followed for 90 days after the last dose of all study drug(s) for AE monitoring, including serious AEs [SAEs] and AEs of special interest [AESI]. Patients who discontinue for reasons other than centrally verified disease progression will have post-treatment follow-up for disease status until disease progression is verified by the central imaging vendor, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All patients will be followed for overall survival until death, the patient withdraws consent, the patient is lost to follow-up, or the study is terminated by the Sponsor. The Sponsor estimates that the study will be fully enrolled within approximately 25 months. Analyses are anticipated at the following times (relative to the first patient's randomization date): approximately 14 months for the first interim analysis, approximately 32 months for the second interim analysis, and approximately 38 to 52 months for the final analysis for overall survival.
Key Eligibility Criteria:	The following list contains key eligibility criteria only; a full list of eligibility criteria is provided in Section 5.0. **Key Inclusion Criteria:** • Provide written, informed consent to participate in the study and follow the study procedures. • Male or female patients, age 18 years or older on the day of signing the informed consent form.

	• Have histologically or cytologically-confirmed recurrent or metastatic HNSCC that is considered incurable by local therapies.
	  o No prior systemic therapy for recurrent or metastatic disease. Systemic therapy given as part of multimodal treatment for locally advanced disease is allowed if completed more than 6 months prior to signing consent.
	  o The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.
	  o Patients may not have a primary tumor site of nasopharynx (any histology) and/or unknown primary.
	• Have measurable disease based on RECIST 1.1 as determined by the local site Investigator. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions since irradiation.
	• Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
	• Tumor tissue from a core, incisional, or excisional biopsy (fine needle aspirates are not acceptable) to the central laboratory for determination of PD-L1 status (if not determined at local laboratory) [redacted]. A newly obtained biopsy is strongly preferred, but archival tumor biopsy may be used and provided (see Section 8.3.1).
	• The tumor must have positive PD-L1 expression (ie, CPS ≥ 1) as determined with the PD-L1 IHC 22C3 PharmDx diagnostic kit at either a local or central laboratory.
	• Patients with oropharyngeal cancer: must have results from testing of HPV status defined as p16 IHC testing using CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ). If HPV status was previously tested using this method, no additional testing is required. Note:
	  o If local p16 testing results are not available, or cannot be assessed by the specified method, a tumor tissue sample may be submitted to the central laboratory for p16 testing.
	Patients with oral cavity, hypopharynx, or larynx cancers: HPV testing by p16 IHC is not required as by convention these tumor locations are assumed to be HPV negative.
	Key Exclusion Criteria:
	• Has disease that is suitable for local therapy administered with curative intent.
	• Has progressive disease within 6 months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC.
	• Has had radiation therapy (or other non-systemic therapy) within 2 weeks prior to initiation of study drug, or patient has not fully recovered (ie, ≤ Grade 1 or at baseline) from AEs due to a previously administered treatment. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-central nervous system (CNS) disease. Note:
	  o Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and qualify for the study.
	  o If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
	• Has a life expectancy of less than 3 months and/or has rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) as determined by Investigator.
	• Has a known additional malignancy that is progressing or has required active treatment within 5 years prior to the first dose of study drug with the exception of: curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, curatively resected in situ cervical cancer, and curatively resected in situ breast cancer.

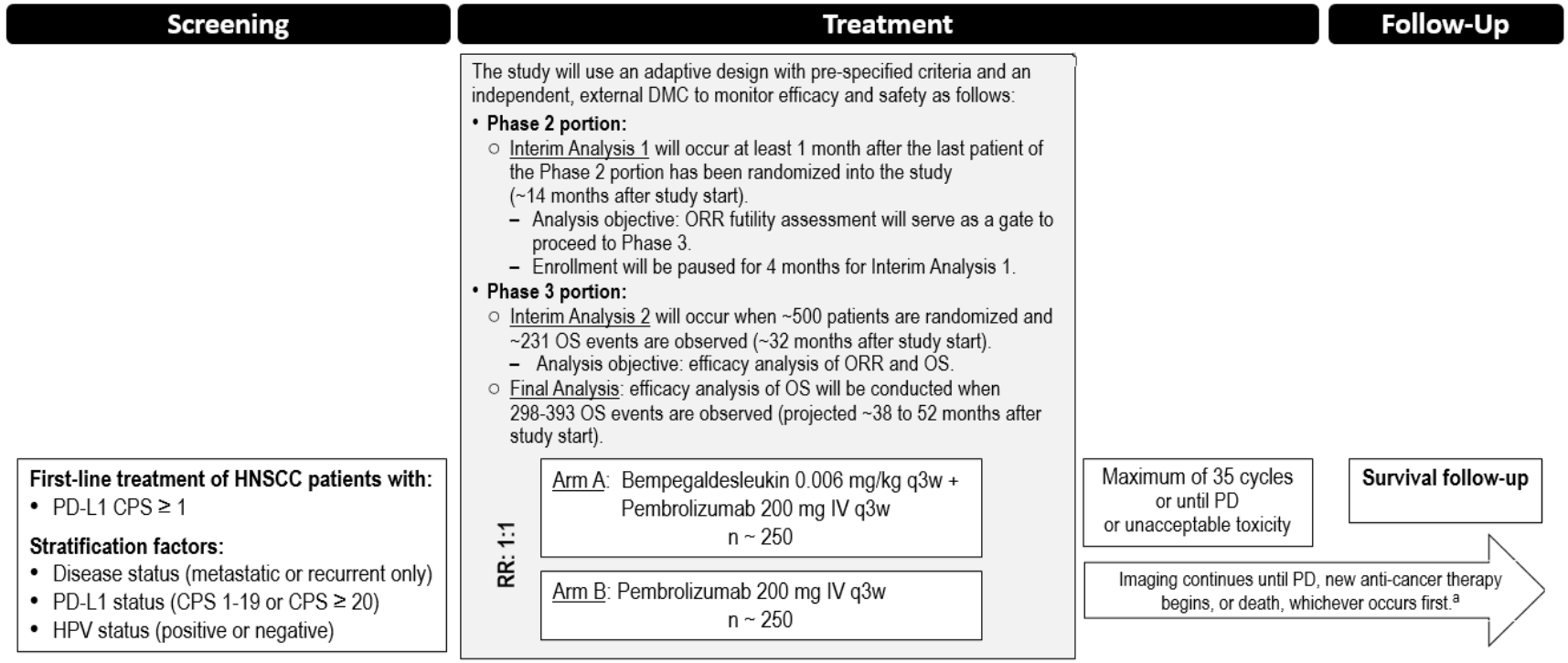
	• Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed. • Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. Corticosteroid use as pre-medication for allergic reactions (eg, intravenous [IV] contrast) is allowed. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
Test Product, Dose and Mode of Administration:	• Bempegaldesleukin 0.006 mg/kg intravenous (IV) infusion every 3 weeks (q3w) • Pembrolizumab 200 mg IV infusion q3w
Comparator Product, Dose and Mode of Administration:	• Pembrolizumab 200 mg IV infusion q3w
[redacted]	[redacted]
Pharmacokinetic and Immunogenicity Evaluation:	Blood samples for PK and immunogenicity will be collected from patients at multiple scheduled sampling times. Validated or qualified methods will be used to measure plasma concentrations of bempegaldesleukin related molecules and serum concentrations of pembrolizumab and ADA. PK parameters will be estimated from plasma or serum concentration-time data where possible. Incidence of ADA will be determined by measurements of anti-bempegaldesleukin, anti-interleukin-2 (anti-IL-2), anti-polyethylene glycol, and anti-pembrolizumab antibodies. Immunogenicity will be reported for ADA positive status and ADA negative status, relative to baseline. Presence of neutralizing antibody may be reported, if applicable.
Efficacy Evaluation:	All response and progression endpoints will be determined by BICR using RECIST 1.1. In the first year from the date of randomization, tumor assessments will be performed every 6 weeks (± 7 days) or more frequently if clinically indicated. One year after randomization, patients who remain on treatment will have imaging performed every 9 weeks (± 14 days). This imaging schedule should be maintained regardless of study treatment delay. Continue to perform imaging until the initial site-assessed disease progression is verified by BICR and confirmed by a repeat BICR assessment ≥ 4 weeks later. Clinically stable patients with unconfirmed disease progression can remain on treatment at the discretion of the Investigator until progression is confirmed with repeated imaging performed ≥ 4 weeks later.
Patient-Reported Outcomes:	Patient-reported outcome (PRO) questionnaires, EORTC QLQ-C30, EORTC QLQ-H&N35, and EuroQol EQ-5D, will be administered by trained site personnel and completed by patients according to the Schedule of Events. It is a best practice and strongly recommended that PROs are administered to randomized patients prior to study drug administration, AE evaluation, and disease status notification. Global health status/quality of life assessment is based on the global health status/quality of life scales of the EORTC QLQ-C30; pain is based on the pain multi-item scales of the EORTC QLQ-H&N35, and time to deterioration in swallowing (ie, the time from baseline

	to first onset of PRO deterioration with confirmation), is based on the swallowing multi-item scales of the EORTC QLQ-H&N35. Opioid analgesic use will be measured based on reported concomitant medications.
Safety Evaluation:	Assessment of safety will be determined by an ongoing review of the following: • Treatment-emergent AEs, including treatment-related AEs, serious AEs (SAEs), AEs of special interest for bempegaldesleukin, events of clinical interest (ECIs) for pembrolizumab, and AEs leading to drug discontinuation. • Clinical laboratory tests (see Appendix 1). • Vital signs. • Physical examination.
Statistical Methods:	**General Considerations:** In general, continuous data will be summarized by descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of patients. **Efficacy:** As a primary efficacy endpoint, ORR will be tested at an alpha level of 0.001 The Cochran Mantel Haenszel (CMH) test statistic will be used to compare the proportion of patients with an objective response between the 2 treatment arms. As a primary efficacy endpoint, OS will be evaluated at an alpha level of 0.049 if ORR is not significant and 0.05 if ORR is significant. The stratified log-rank test statistic with prespecified weights will be used to compare OS between the 2 treatment arms. A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the hazard ratio and corresponding 95% confidence interval (CI). The Kaplan-Meier method will be used to further summarize OS, including Kaplan-Meier curves, medians with corresponding 95% CIs, etc. The first interim analysis will occur at least one month after the last patient of the Phase 2 portion has been randomized into the study. At the first interim analysis, ORR will be assessed for futility: • ORR futility assessment (ie, difference in ORR proportions is ≥ 0% [bempegaldesleukin plus pembrolizumab minus pembrolizumab monotherapy]) will serve as a gate to proceed to the Phase 3 portion of the study. If the DMC determines that the study should continue based on the prespecified futility boundary, Phase 3 of the study will begin following an expected 4-month enrollment pause for the first interim analysis readout. At the second interim analysis when approximately 500 patients have been randomized and about 231 OS events have been observed, the following tests will be conducted (if the actual number of events at the time of the analysis is different from the planned one, the actual alpha and statistical significance level will be adjusted using O'Brien and Fleming alpha spending function): • If ORR is not significant at the second interim analysis, OS will be tested at an overall alpha level of 0.049 and at $\alpha = 0.021$ at the second interim analysis. • If ORR is significant at the second interim analysis, the fallback method will be used and OS will be tested at an overall alpha level of 0.05 at $\alpha = 0.022$ at the second interim analysis. For the final analysis, the adaptive method in Liu and Hu (Liu 2016) and Mehta and Pocock (Mehta 2011) will be used to determine the number of OS events needed to target approximately 85% to 90% conditional power for the final analysis. The minimum and maximum number of OS events for the final analysis are 298 and 393, respectively. At the final analysis, the primary analysis of OS to claim statistical significance will be based on the weighted combination version of the stratified log-rank test with prespecified weights (Lehmacher 1999). Statistical significance level for the final analysis is 0.043 or 0.044 depending on whether ORR is significant at the second interim analysis. Prespecified

	weights for the primary OS are $w = \sqrt{231/345}$ and 1-w for events occurring before and after the second interim analysis, respectively. The middle point, 345, of minimum and maximum event sizes is chosen to set up the weights. The conventional stratified log-rank test with equal weights for every patient will be conducted as a sensitivity analysis. Details will be provided in the Statistical Analysis Plan. **Safety:** Overall safety and tolerability of bempegaldesleukin plus pembrolizumab will be measured by the incidence of AEs, AESIs, SAEs, deaths, and laboratory abnormalities. Safety analyses will be summarized for the Safety population using descriptive statistics by treatment arm.

1.1 Study Schematic

Figure 1: Study Schematic



Abbreviations: ~ = approximately; CPS = combined positive score; DMC = Data Monitoring Committee; HNSCC = head and neck squamous-cell carcinoma; HPV = human papillomavirus; IV = intravenous; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed cell death ligand 1; q3w = every 3 weeks; RR = randomization ratio

Note: The study schematic describes the initial treatment (ie, First Course). See Section 6.2.6 for information regarding eligibility for a Second Course.

a. Additional reasons for discontinuing imaging are withdrawal of consent and the end of the study (see Section 8.1.2).

1.2 Schedule of Events

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

Procedure / Period:	Screening	Treatment Cycles (3-Week Cycles)					Post-treatment		
		Cycle 1 Only			Cycle 2 and Beyond		Follow-up Visit 1[y]	Follow-up Visit 2[y]	Survival Follow-up[z]
Study Days[a]:	Day –28 to –1	Day 1	Day 3 (– 1 day)	*Phase 3 only:* Day 5 (± 1 day)	Day 1 (± 3 days)	Day 3 (+ 2 days)	30 days from last dose (± 7 days)	90 days from last dose (± 7 days)	Every 12 weeks (± 14 days)
Informed consent	X								
Inclusion/ exclusion criteria	X								
Demographics and medical history[b]	X								
Tumor biopsy[c]	X								
Randomization		X[d]							
Physical examination[e]	X	Predose			Predose		X	X	
Vital signs[f]	X	X[f]	X		X[f]		X	X	
ECOG performance status[g]	X	Predose			Predose		X	X	
ECG[h]	X								
ECHO/MUGA[i]	X								
Pregnancy test[j]	X[j]	Predose[j]			Predose		X	X	
Hematology and serum chemistry[k]	X	Predose			Predose		X		
Coagulation[k]	X								
Thyroid function tests (T3 [total or free], free T4, TSH)[l]	X				Predose[l]		X		

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

Procedure / Period:	Screening	Treatment Cycles (3-Week Cycles)					Post-treatment		
		Cycle 1 Only			Cycle 2 and Beyond		Follow-up Visit 1[y]	Follow-up Visit 2[y]	Survival Follow-up[z]
Study Days[a]:	**Day −28 to −1**	**Day 1**	**Day 3 (− 1 day)**	***Phase 3 only:* Day 5 (± 1 day)**	**Day 1 (± 3 days)**	**Day 3 (+ 2 days)**	**30 days from last dose (± 7 days)**	**90 days from last dose (± 7 days)**	**Every 12 weeks (± 14 days)**
Additional lab assessments[m]	X				Predose[m]				
Urinalysis (dipstick)[n]	X	Predose			Predose				
Serology[o]	X								
Tumor HPV status[p]	X								
PK and immunogenicity assessments		***Phase 2 portion of the study:*** refer to Table 8 ***Phase 3 portion of the study:*** refer to Table 9							
[redacted]		[redacted]							
Tumor assessment[q]	X	First year from date of randomization, imaging every 6 weeks (± 7 days), or more frequently if clinically indicated. After 1 year from randomization, imaging every 9 weeks (± 14 days) for patients who remain on treatment.					For patients who discontinue study drug without progression, monitor every 6 weeks (± 7 days) (or every 9 weeks ± 14 days 1 year after randomization) until: 1) Start of new anticancer treatment, 2) Disease progression by BICR, 3) Death, 4) Withdrawal of consent, or 5) End of the study, whichever occurs first. The first follow-up assessment should occur 6 weeks (± 7 days) from the last scheduled on-treatment imaging time point (or 9 weeks ±14 days from the last scheduled on–treatment imaging time point 1 year after randomization).		

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

Procedure / Period:	Screening	Treatment Cycles (3-Week Cycles)					Post-treatment		
		Cycle 1 Only			Cycle 2 and Beyond		Follow-up Visit 1[y]	Follow-up Visit 2[y]	Survival Follow-up[z]
Study Days[a]:	Day −28 to −1	Day 1	Day 3 (− 1 day)	*Phase 3 only:* Day 5 (± 1 day)	Day 1 (± 3 days)	Day 3 (+ 2 days)	30 days from last dose (± 7 days)	90 days from last dose (± 7 days)	Every 12 weeks (± 14 days)
Arm A (bempegaldesleukin plus pembrolizumab) only:									
Local lab assessments prior to dosing[r]		Predose			Predose				
Administer IV fluids[s]		X			X				
Premedications[t]		Predose			Predose				
Oral hydration follow-up			X[u]			X[u]			
Study drug administration[v]		X			X				
AE assessment	X	At every visit					X	X	
Review of concomitant medications/procedures	X	At every visit					X	X	
Health-related quality of life assessments[w]		Predose			Predose		X		
Subsequent anticancer therapy[x]							X	X	X
Follow-up visits[y]							X	X	
Survival follow-up[z]									X

Abbreviations: AE = adverse event; BICR = blinded independent central review; ctDNA = circulating tumor deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D = EuroQol EQ-5D questionnaire; HPV = human papillomavirus; IV = intravenous; min = minutes; MUGA = multigated acquisition; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

a. Cycle intervals less than 21 days (eg, 21 days - 3 days) should only occur if the Investigator believes there are no safety concerns with dosing the patient 1 to 3 days prior to a 21-day cycle. All procedures and examinations should be performed before the administration of study drug(s), except as indicated. 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, the coronavirus disease 2019 (COVID-19) public health emergency, or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation. Following randomization, Investigators may choose to perform study visits via telemedicine or at alternate locations if needed during periods of global pandemics (eg, COVID-19); however, any protocol-mandated procedures that cannot be performed via telemedicine or at alternate locations will be documented as a protocol deviation.

b. A medical history will be obtained by the Investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that is considered to be clinically significant by the Investigator. The patient's history of tobacco use will also be collected. Details regarding the patient's head and neck cancer will be recorded separately and not listed as medical history.

c. Tumor tissue requirements: formalin-fixed paraffin-embedded (FFPE) tumor tissue block (obtained within 12 months of randomization) or unstained FFPE tumor tissue sections on slides (a minimum of 8 slides, preferably 15 to 25, obtained within 4 months [if stored in the dark at room temperature up to 25°C] or 6 months [if stored in the dark at 2°C–8°C] of randomization) collected from a recurrent lesion without intervening therapy and irradiation, are acceptable in lieu of a newly obtained excisional, incisional, or core tumor biopsy prior to treatment. Recurrent lesions in a previously irradiated area can be biopsied if progression has been shown in such lesions since irradiation. See Section 8.3.1. Newly obtained biopsies are preferred to archived tissue.
PD-L1 expression: PD-L1 expression testing will be determined by a local or central laboratory. PD-L1 testing will use the PD-L1 IHC 22C3 PharmDx diagnostic kit.

d. Within 5 calendar days following randomization, the patient should receive the first dose of study treatment.

e. Physical examinations must occur within 5 days prior to administering study drug(s). A full physical examination should be conducted during Screening; targeted physical examinations should be conducted on Day 1 of Cycles 1 and beyond and at the post-treatment follow-up visits. See Section 10.19 for additional details.

f. See Section 10.20. Weight is to be reported at each vital sign visit, height at screening only. On dosing days, vital signs are to be taken and recorded as follows:
   - For Arm A (bempegaldesleukin/pembrolizumab): prior to bempegaldesleukin infusion and 30 (± 10) minutes following the end of pembrolizumab infusion.
   - For Arm B (pembrolizumab monotherapy): prior to pembrolizumab infusion and 30 (± 10) minutes following the end of pembrolizumab infusion.

g. ECOG performance status assessments for Day 1 of each cycle must occur within 5 days prior to administering study drug(s) (see Appendix 3). If the Cycle 1 Day ECOG assessment will be performed within 7 days of the Screening assessment, the ECOG assessment will not need to be repeated.

h. ECG must be done within 14 days of the date of randomization. See Section 10.21.

i. A standard echocardiogram or MUGA must be performed for all patients within 60 days prior to randomization to assess for cardiac function and left ventricular ejection fraction (LVEF). See Section 10.22.

j. Pregnancy test information is provided in Section 10.16.1. Women of childbearing potential (WOCBP) must have a screening negative serum or urine pregnancy test within 28 days prior to randomization. A negative highly sensitive pregnancy test (urine or serum as required by local regulations) is required within 24 hours for urine or within 72 hours for serum before the first dose of study treatment.

k. Screening hematology and chemistry and coagulation must be drawn within 10 days of the date of randomization. Hematology and chemistry assessments for Day 1 of each cycle must be drawn within 5 days prior to administering study drug(s). See Section 10.18 and Appendix 1.

l. See Appendix 1. Screening thyroid function tests must be drawn within 28 days of the date of randomization. Thyroid function tests may be obtained within 5 days of administration of study drugs.

m. See Appendix 1. Screening additional laboratory tests must be drawn within 28 days of the date of randomization. For Cycle 2 and beyond, the sampling for additional laboratory tests can be drawn within 5 days prior to administration of study drug(s). Any patient receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study via local laboratories per institutional guidelines.

n. See Appendix 1. Urinalysis assessment for Day 1 of each cycle must be provided within 5 days prior to administering study drug(s).

o. Screening serology laboratory tests can be drawn within 28 days of the date of randomization. See Appendix 1.

p. For patients with oropharyngeal cancer only: tumor tissue collection for HPV status is described in Section 8.3.1.1.

q. Section 8.1 describes tumor imaging (including confirmation of tumor response) and assessment of disease. All tumor assessments will be sent to the imaging vendor. For patients who continue to receive treatment beyond progression, see Section 6.2.5. For assessments in long-term follow-up, see Section 6.3.

Arm A (bempegaldesleukin plus pembrolizumab) only:

r. See Appendix 1B for the list of local laboratory tests that require evaluation within 24 hours prior to bempegaldesleukin administration or as soon as locally feasible.

s. Hydration guidelines provided in Section 6.2.3.2.

t. See Section 6.7.1 for premedication guidance before study drug infusion(s).

u. In Cycles 1 and 2, site personnel must contact the patient (by telephone or clinic visit) once between Days 3 and 5 (inclusive) following infusion, to remind the patient of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion (see Section 6.2.3.2). In Cycles 3 and beyond, the oral hydration follow-up is conducted as clinically indicated for patients in Arm A receiving bempegaldesleukin and pembrolizumab.

v. Within 5 calendar days following randomization, the patient should receive the first dose of study treatment. Study drug infusion timing should be as close to 30 minutes as possible; however, a window between −5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes −5 min/+10 min). See Sections 6.2.2.1 and 6.2.2.2 for additional details.

w. At each visit specified, health-related quality of life assessments should be performed in the following order: EQ-5D first, then European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), and finally the EORTC Quality of Life Questionnaire-head and neck cancer specific module (QLQ-H&N35). The questionnaires will be completed prior to dosing at Cycle 1, Cycle 2, Cycle 3, Cycle 4 and every 2 cycles thereafter (eg, Cycle 6, Cycle 8, Cycle 10) up to 1 year from treatment initiation or End of Treatment, whichever occurs first, and at the Follow-up Visit 1. See Section 9.2.

x. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression to subsequent anticancer therapies will be collected.

y. For Follow-up visits, see Section 6.3.1.

z. For Survival Follow-up, see Section 6.3.2.

Table 2: Second Course Phase – Retreatment with Study Drug: Schedule of Events

Procedure / Period:	Treatment Cycles (3-Week Cycles)						Post-treatment		
					To be repeated beyond 6 cycles				
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Follow-up Visit 1[p]	Follow-up Visit 2[p]	Survival Follow-up[q]
Study Days[a]:	**+ 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**30 days from last dose (± 7 days)**	**90 days from last dose (± 7 days)**	**Every 12 weeks (± 14 days)**
Eligibility criteria[b]	X								
Physical examination[c]	Predose	Predose	Predose	Predose	Predose	Predose	X	X	
Vital signs[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X	X	
ECOG performance status[e]	Predose	Predose	Predose	Predose	Predose	Predose	X	X	
Pregnancy test[f]	Predose[f]	Predose	Predose	Predose	Predose	Predose	X	X	
Hematology and serum chemistry[g]	Predose	Predose	Predose	Predose	Predose	Predose	X		
Thyroid function tests (T3 [total or free], free T4, TSH)[h]	Predose		Predose		Predose		X		
Coagulation[h]	Predose								
Additional lab assessments[h]	Predose	Predose	Predose	Predose	Predose	Predose			
Tumor assessment[i]	Imaging should continue to be performed every 6 weeks (± 7 days) from the first dose of study drug(s) in the Second Course or more frequently if clinically indicated.								

Table 2: Second Course Phase – Retreatment with Study Drug: Schedule of Events (Contd)

Procedure / Period:	Treatment Cycles (3-Week Cycles)						Post-treatment		
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Follow-up Visit 1[p]	Follow-up Visit 2[p]	Survival Follow-up[q]
Study Days[a]:	+ 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	30 days from last dose (± 7 days)	90 days from last dose (± 7 days)	Every 12 weeks (± 14 days)
Arm A (bempegaldesleukin plus pembrolizumab) only:									
Local lab assessments prior to dosing[j]	Predose	Predose	Predose	Predose	Predose	Predose			
Administer IV fluids[k]	X	X	X	X	X	X			
Premedications[l]	Predose	Predose	Predose	Predose	Predose	Predose			
Oral hydration follow-up[m]	X[m]	X[m]							
Study drug administration[n]	X	X	X	X	X	X			
AE assessment	X	At every visit					X	X	
Review of concomitant medications/procedures	X	At every visit					X	X	
Subsequent anticancer therapy[o]							X	X	X
Follow-up visits[p]							X	X	
Survival follow-up[q]									X

Abbreviations: AE = adverse event; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; min = minutes; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

a. Cycle intervals less than 21 days (eg, 21 days - 3 days) should only occur if the Investigator believes there are no safety concerns with dosing the patient 1 to 3 days prior to a 21-day cycle. All procedures and examinations should be performed before the administration of study drug(s), except as indicated. 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, the coronavirus disease 2019 (COVID-19) public health emergency, or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation. Following randomization, Investigators may choose to perform study visits via telemedicine or at alternate locations if needed during periods of global pandemics (eg, COVID-19); however, any protocol-mandated procedures that cannot be performed via telemedicine or at alternate locations will be documented as a protocol deviation.

b. Patients who either (1) attain a complete response and discontinue treatment OR (2) discontinue treatment after 35 cycles (approximately 2 years of study) for reasons other than disease progression or intolerability may restart trial treatment if they meet the criteria specified in Section 6.2.6.

c. Physical examinations must occur within 5 days prior to administering study drug(s). A full physical examination should be conducted in Cycle 1; targeted physical examinations should be conducted on Day 1 of Cycles 2 and beyond and at the posttreatment follow-up visits. See Section 10.19 for additional details.

d. See Section 10.20. Weight is to be reported at each vital sign visit. On dosing days, vital signs are to be taken and recorded as follows:
   - For Arm A (bempegaldesleukin/pembrolizumab): prior to bempegaldesleukin infusion and 30 (± 10) minutes following the end of pembrolizumab infusion.
   - For Arm B (pembrolizumab monotherapy): prior to pembrolizumab infusion and 30 (± 10) minutes following the end of pembrolizumab infusion.

e. ECOG performance status assessments for Day 1 of each cycle must occur within 5 days prior to administering study drug(s) (see Appendix 3).

f. Pregnancy test information is provided in Section 10.16.1. A negative highly sensitive pregnancy test (urine or serum as required by local regulations) is required within 24 hours for urine or within 72 hours for serum before the first dose of study treatment.

g. Hematology and chemistry assessments for Day 1 of each cycle must be drawn within 5 days prior to administering study drug(s). See Section 10.18 and Appendix 1.

h. See Appendix 1. The sampling for thyroid function, coagulation, and additional laboratory tests can be drawn within 5 days prior to administration of study drug(s). Any patient receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study via local laboratories per institutional guidelines.

i. Section 8.1 describes tumor imaging (including confirmation of tumor response) and assessment of disease. A scan must be performed within 28 days prior to restarting treatment. Imaging should continue to be performed every 6 weeks (± 7 days) from the first dose of Second Course trial treatment or more frequently if clinically indicated. All tumor assessments will be sent to the imaging vendor. For patients who continue to receive treatment beyond progression, see Section 6.2.5. For assessments in long-term follow-up, see Section 6.3.

Arm A (bempegaldesleukin plus pembrolizumab) only:

j. See Appendix 1B for the list of local laboratory tests that require evaluation within 24 hours prior to bempegaldesleukin administration or as soon as locally feasible.

k. Hydration guidelines provided in Section 6.2.3.2.

l. See Section 6.7.1 for premedication guidance before study drug infusion(s).

m. In Cycles 1 and 2, site personnel must contact the patient (by telephone or clinic visit) once between Days 3 and 5 (inclusive) following infusion, to remind the patient of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion (see Section 6.2.3.2). In Cycles 3 and beyond, the oral hydration follow-up is conducted as clinically indicated for patients in Arm A receiving bempegaldesleukin and pembrolizumab.

n. Patients who restart treatment should resume with the same study drug(s) and at the same dose that they were receiving prior to discontinuation. Study drug infusion timing should be as close to 30 minutes as possible; however, a window between −5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes −5 min/+10 min). See Sections 6.2.2.1 and 6.2.2.2 for additional details.

o. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression to subsequent anticancer therapies will be collected.

p. For Follow-up visits, see Section 6.3.1.

q. For Survival Follow-up, see Section 6.3.2.

2.0 INTRODUCTION

This is a Phase 2/3, randomized study of bempegaldesleukin combined with pembrolizumab or pembrolizumab monotherapy in patients with recurrent or metastatic head and neck cancer that is previously untreated. Approximately 500 patients with first-line recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) will be randomized in a 1:1 ratio between the 2 arms of the study to examine the efficacy and safety of bempegaldesleukin plus pembrolizumab (Arm A) versus pembrolizumab monotherapy (Arm B).

2.1 Background

2.1.1 HNSCC / Current Therapies

Head and neck cancer describes a range of tumors that arise in the head and neck region, which includes the oral cavity, oropharynx, hypopharynx, and larynx. The worldwide incidence of head and neck cancer approaches 750,000 cases annually, ranking it as the eighth most common cancer, accounting for nearly 4% of all malignancies in the world (Sung 2021) and 3.5% of all malignancies in the United States (Siegel 2021). Although the head and neck region has a wide diversity of structures and cell types, the vast majority of head and neck cancers arise from the mucosa of the upper aerodigestive tract and are predominantly squamous cell in origin.

A large number of patients with head and neck cancer initially present with locally advanced, Stage 3 or 4 disease that is initially treated with combinations of chemotherapy, radiation and/or surgery. This initial treatment is generally designated as “definitive” therapy, which typically combines chemoradiation and surgery and can result in disease control rates ranging between 33% and 86% of patients. Patients who progress after initial definitive therapy require subsequent treatment for recurrent disease. Patients who initially present with metastatic disease generally receive the same therapy as those with recurrent disease after definitive treatment.

Based on the results of the Phase 3 KEYNOTE-048 study, pembrolizumab was established as an appropriate first-line treatment for patients with recurrent or metastatic HNSCC and tumors with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥ 1 (see Section 2.1.2.2).

2.1.2 Pembrolizumab

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

2.1.2.1 Pembrolizumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on

cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses (Pardoll 2003; Zitvogel 2006; Dunn 2002). Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR) (Greenwald 2005). Collectively, these signals govern the balance between T-cell activation and tolerance.

Programmed cell death protein 1 (PD-1) is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4 (cytotoxic T lymphocyte-associated protein 4), inducible T-cell co-stimulator (ICOS), and B- and T-lymphocyte attenuator (BTLA; Freeman 2000). PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of interleukin-2 (IL-2), IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also has been noted to inhibit T-cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes (Sharpe 2007). These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (Dong 2002; Sharpe 2002; Brown 2003; Francisco 2010; Thompson 2007). In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells / FoxP3+ regulatory T cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in multiple models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of

effector T-cell function in vivo (Ropponen 1997; Dudley 2005; Hunder 2008; Polcher 2010; Okazaki 2001; Greenwald 2005; Chow 2015). Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the pembrolizumab Investigator's Brochure).

2.1.2.2 Pembrolizumab in Clinical Trials in Patients with HNSCC

Ongoing clinical trials are being conducted in advanced melanoma, non-small cell lung cancer (NSCLC), a number of advanced solid tumor indications (including head and neck cancer), and hematologic malignancies. For study details, please refer to the pembrolizumab Investigator's Brochure.

The Phase 3 KEYNOTE-048 study established pembrolizumab as an appropriate first-line treatment for patients with recurrent or metastatic HNSCC and tumors with PD-L1 CPS ≥ 1. In this study, pembrolizumab monotherapy (200 mg every 3 weeks [q3w]) improved overall survival (OS) versus cetuximab and chemotherapy in patients with CPS ≥ 20 (median 14.9 months vs 10.7 months, hazard ratio [HR] 0.61 [95% CI 0.45–0.83] p-value = 0.0007) and in patients with CPS ≥ 1 (12.3 vs 10.3, HR 0.78 [95% CI: 0.64–0.96], p-value = 0.0086) and was non-inferior in the total population (11.6 vs 10.7, 0.85 [0.71−1.03]). At the final analysis, the objective response rate (ORR) in the PD-L1 CPS ≥ 20 population was 23% and 36% in the pembrolizumab monotherapy and cetuximab with chemotherapy groups, respectively, and the ORR in the CPS ≥ 1 population was 19% and 35%, respectively (Burtness 2019).

Other trials evaluating pembrolizumab in head and neck cancer have demonstrated clinical activity in patients with recurrent and/or metastatic disease, including those with poor prognosis.

- KEYNOTE-012 was a Phase 1b study of pembrolizumab in 4 indications, one of which included patients with head and neck cancer. Single-agent pembrolizumab demonstrated clinically meaningful anti-tumor activity in patients with PD-L1-positive, (ie, any level of PD-L1 expression, defined as ≥ 1% of tumor cells or stroma that were PD-L1-positive by immunohistochemistry [IHC]), recurrent or metastatic HNSCC, with an overall response of 18% (8 of 45 patients; 95% CI 8-32) and 25% (4 of 16; 7-52) in human papillomavirus (HPV)-positive patients and 14% (4 of 29; 4-32) in HPV-negative patients (Seiwert 2016).
- KEYNOTE-040 was a Phase 3, multicenter, randomized trial of pembrolizumab (200 mg q3w) versus standard of care in subjects with recurrent or metastatic HNSCC. Results from KEYNOTE-040 showed that pembrolizumab imparted a greater benefit in subjects with PD-L1 expressing tumors. In the CPS ≥ 1 population, the ORR was 17.3% for the pembrolizumab arm compared to 9.9% for the standard of care arm (CI: 0.6% to 14.6%). The median OS was 8.7 months for the pembrolizumab arm compared to 7.1 months for the standard of care arm (HR=0.75, CI: 0.59-0.95) (Cohen 2017).

- KEYNOTE-055 was a Phase 2 study of 171 patients with recurrent or metastatic HNSCC who were previously treated with platinum and cetuximab. In this population with poor prognosis, pembrolizumab 200 mg q3w exhibited clinically meaningful antitumor activity, including an ORR of 16% (95% CI 11% to 23%), a median response duration of 8 months (range, 2+ to 12+ months), a median progression-free survival (PFS) of 2.1 months, and median OS of 8 months (Bauml 2017).

2.1.3 Bempegaldesleukin (NKTR-214)

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

2.1.3.1 Mechanism of Action

Bempegaldesleukin (NKTR-214) is a prodrug of a conjugated cancer immunotherapy cytokine that exerts its biological activity by binding to the IL-2 receptor and subsequent activation of effector T cells. As a PEGylated human recombinant IL-2 molecule of aldesleukin with an average of six releasable polyethylene glycol (PEG) chains, bempegaldesleukin can be administered conveniently in the outpatient setting using an antibody-like dosing regimen. The polymer conjugation renders the cytokine initially inactive. Upon intravenous (IV) administration, the PEG chains slowly release to generate the active cytokine species (mainly 2-PEG-IL-2 and 1-PEG-IL-2) that have a peak plasma concentration of 24 to 48 hours after infusion. The slow generation of the 2-PEG-IL-2 and 1-PEG-IL-2 significantly mitigates the rapid-onset, systemic cytokine-related toxicities associated with high dose IL-2.

The polymer conjugation of bempegaldesleukin promotes biased signaling through the IL-2 receptor beta gamma (IL-2Rβγ). Specifically, the location of the bempegaldesleukin PEG chains interferes with the binding to the IL-2 alpha receptor subunit responsible for the undesirable effect of activating regulatory T cells (Tregs) in the tumor while continuing to permit binding to the IL-2Rβγ (CD122) receptor. Upon infusion, bempegaldesleukin preferentially increases the proliferation, activation, and effector function of tumor antigen-specific CD8+ T cells and natural killer (NK) cells within the tumor microenvironment (TME) over expansion of unwanted intra-tumoral Tregs that are activated through the IL-2 receptor alpha beta gamma (IL-2Rαβγ) (Charych 2016a; Charych 2016b). Consistent with this mechanism of action, recent nonclinical studies demonstrate strong synergy of bempegaldesleukin with adoptive T-cell therapy (ACT), with PD-1 checkpoint blockade, and with tumor antigen-specific vaccination, in a variety of mouse models (Parisi 2020; Sharma 2020). This synergy was mediated by expansion of tumor-specific CD8+ T cells in the periphery and tumor, without strong expansion of Tregs in the tumor tissue.

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

The immunological properties of bempegaldesleukin with the induction of TILs and upregulation of the PD-1/PD-L1 axis makes bempegaldesleukin a potentially promising combination therapy

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

2.1.3.2 Clinical Experience with Bempegaldesleukin

2.1.3.2.1 Study 15-214-01 (EXCEL) Bempegaldesleukin Monotherapy

The bempegaldesleukin clinical development program started with the monotherapy study EXCEL (Study 15-214-01 [NCT02869295]; A Phase 1/2, Open-label, Multicenter, Dose-Escalation and Dose Expansion Study of NKTR-214 in Subjects with Locally Advanced or Metastatic Solid Tumor Malignancies). The first part of the study was a dose escalation phase, designed to evaluate the safety and tolerability, and define the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of bempegaldesleukin. The second part of the study was an expansion phase following identification of the RP2D, designed to evaluate the safety and tolerability, as well as the efficacy of bempegaldesleukin in specific tumor types. Bempegaldesleukin at a dose of 0.009 mg/kg administered once every 3 weeks was deemed the MTD by pre-defined dose-limiting toxicity criteria. The RP2D was determined to be 0.006 mg/kg q3w. Enrollment was closed after 28 patients were exposed to bempegaldesleukin in the dose-escalation phase and the dose expansion phase was not initiated.

The safety of single-agent bempegaldesleukin has been assessed in 28 patients across 5 dose cohorts administered bempegaldesleukin q3w at doses ranging from 0.003 mg/kg to 0.012 mg/kg and a dosing frequency of every 2 weeks (q2w) was explored at 0.006 mg/kg. For the q3w dosing frequency, doses up to 0.009 mg/kg were well tolerated. One patient dosed at 0.012 mg/kg experienced cytokine release syndrome and the dose-limiting toxicities (DLTs) of hypotension and syncope; this patient received 2 additional cycles of bempegaldesleukin at a lower dose of 0.006 mg/kg and tolerated treatment well. The bempegaldesleukin dose of 0.009 mg/kg was determined to be the MTD.

As of the final database lock date of 29 March 2018, 593 treatment-emergent adverse events (AEs) were reported among the 28 patients who received single-agent bempegaldesleukin. Overall, the most common treatment-emergent AEs were fatigue (82.1%), flu-like symptoms (also consisting of influenza-like illness, influenza, pyrexia, and chills, 71.4%), pruritus (67.9%), hypotension (64.3%), rash (consisting of erythema, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, rash generalized, and rash macular, 53.6%), decreased appetite (53.6%), and arthralgia or cough (42.9% each).

The most common AEs considered by the Investigator to be related to bempegaldesleukin were fatigue (71.4%), flu-like symptoms (67.9%), pruritus (64.3%), hypotension (57.1%), rash (50.0%), decreased appetite (46.4%), and arthralgia or cough (32.1% each). Such treatment-related AEs as flu-like symptoms, rash and pruritus were generally mild or moderate in severity, predictable, manageable, and short-lived. These cytokine-related AEs generally

occurred 3 to 4 days after dosing and corresponded to the time of peak plasma concentration of the active cytokines. The flu-like symptoms were managed with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) and the cases of rash/pruritus were either self-limiting or treated with antihistamines (steroids were administered for occasional patients who had severe rash/pruritus).

Six of 28 patients reported Grade 3 treatment-related AEs, which included hypotension, abdominal pain, infusion-related reaction, headache, and syncope. The cases of Grade 3 hypotension were rapidly reversed with intravenous fluids, and a hydration management guideline was implemented during the study which mitigated the incidences of hypotension and/or severity. One patient, who had a prior history of an infusion reaction to a previously administered immunotherapy, discontinued treatment due to an infusion-related reaction following the first dose of bempegaldesleukin 0.009 mg/kg. With the exception of one event of hypothyroidism, no other known immune mediated AEs consistent with checkpoint inhibitors were reported. No patient experienced capillary leak syndrome and no Grade 4 treatment-related AEs or treatment-related deaths were reported on the study.

Fifteen patients (53.6%) reported 31 serious AEs (SAEs) in monotherapy Study 15-214-01. Eleven SAEs reported among 7 (25.0%) patients were considered related to treatment. The only treatment-related SAE reported for more than 1 patient was hypotension (5 patients, 17.9%, 4 of 5 were Grade 3 in severity).

In the 28 patients evaluable for efficacy in Study 15-214-01, best overall response included stable disease in 14 patients (50%), 12 patients (42.9%) with progressive disease (PD) and 2 patients (7.1%) were not evaluable (NE). While no objective responses were observed in Study 15-214-01, 9 patients experienced tumor shrinkage between 1% and 30% and two patients, after progressing on multiple prior therapies, had durable stable disease over 1 year. One patient with metastatic melanoma, who was previously treated with ipilimumab and a BRAF inhibitor, received 25 cycles of bempegaldesleukin and had durable stable disease for 18 months. A second patient with metastatic renal cell carcinoma (RCC), who had progressed on high-dose IL-2 and was refractory to single-agent OX40 (ie, an antibody targeting the tumor necrosis factor receptor superfamily member 4) and nivolumab, was treated with 19 cycles of bempegaldesleukin and had durable stable disease for 14 months. Given the biological properties of bempegaldesleukin and nivolumab these observations further supported the rationale for combining these two agents.

2.1.3.2.2 Study 16-214-02 (PIVOT-02) Bempegaldesleukin and Nivolumab Combination Therapy

The PIVOT-02 trial (NCT02983045) is an ongoing Phase 1/2 open-label, multicenter, dose escalation, and dose expansion study of bempegaldesleukin in combination with nivolumab and other anticancer therapies in patients with locally advanced or metastatic solid tumors. Part 1 of the study was a dose escalation phase to evaluate the safety and tolerability, and define the MTD or RP2D of bempegaldesleukin in combination with nivolumab. Following determination of the

RP2D (0.006 mg/kg bempegaldesleukin q3w plus 360 mg nivolumab q3w), Part 2 of the study is evaluating the safety and tolerability as well as the efficacy of the combination by assessing the ORR at the RP2D. The indications studied in Part 2 include melanoma, RCC, NSCLC, urothelial carcinoma, breast cancer, gastric cancer, colorectal carcinoma (CRC), and small cell lung cancer (SCLC). Parts 3 and 4 are schedule-finding and dose expansion for the triplet, studying the safety and tolerability of bempegaldesleukin in combination with nivolumab and ipilimumab in patients with metastatic RCC, urothelial carcinoma, melanoma, or NSCLC who are treatment-naïve.

The bempegaldesleukin and nivolumab dose escalation portion of PIVOT-02 has completed, with the safety results of bempegaldesleukin at 0.006 mg/kg in combination with nivolumab 360 mg every 3 weeks indicating no DLTs and no Grade ≥ 3 treatment-related AEs at the time of completion. Bempegaldesleukin 0.006 mg/kg in combination with nivolumab 360 mg every 3 weeks was the recommended dose regimen to be taken forward into expansion cohorts in Part 2.

As of 28 October 2019, a total of 541 patients have been treated with bempegaldesleukin in combination with nivolumab (488 patients with doublet [bempegaldesleukin and nivolumab]; 43 patients with triplet [bempegaldesleukin, nivolumab, and ipilimumab]; and 10 patients with doublet [bempegaldesleukin and nivolumab] plus other anticancer study drug). The median duration of exposure was 115.0 days (doublet, 112.0; triplet, 151.0; doublet plus other anticancer drug, 137.5) (range: 6 to 815 days).

Among the 488 patients who received the doublet, the most frequently reported treatment-emergent AEs were fatigue (52.9%), pyrexia (50.2%), nausea (39.5%), pruritus (38.5%), decreased appetite (36.3%), diarrhea or rash (each 28.5%), chills (28.3%), influenza-like illness (27.5%), arthralgia (26.4%), and cough or vomiting (each 25.2%).

The most frequently reported treatment-related AEs in the 488 patient doublet group were fatigue (47.3%), pyrexia (44.3%), pruritus (35.7%), nausea (29.7%), influenza-like illness (26.8%), decreased appetite (26.4%), chills (26.0%), and rash (25.8%).

Among the 488 patients treated with the doublet, the most frequently reported treatment-emergent AEs Grade ≥ 3 were dyspnea (3.9%), anemia or hyponatremia (each 3.7%), hypotension or syncope (each 3.5%), fatigue or urinary tract infection (each 2.7%), and hypertension or lipase increased (each 2.5%). The Grade ≥ 3 treatment-related AEs experienced by 2.0% or more patients in the doublet group were syncope (2.9%), hypotension (2.7%), and lipase increased (2.0%).

As of 28 October 2019, 44.7% of doublet patients have reported SAEs; the most frequently experienced SAEs were pyrexia (3.7%), dyspnea or hypotension (2.9%), and hyponatremia (2.0%). Treatment-related SAEs were reported for 17.2% of doublet patients, with the most frequently reported being pyrexia (3.1%), hypotension (2.0%), and pneumonitis (1.0%).

Tumor response data are available for 37 of the dose escalation patients, including 11 with metastatic melanoma, 21 with RCC, and 5 with NSCLC. Of these 37 response-evaluable patients, 24 were treated at 0.006 mg/kg bempegaldesleukin combined with nivolumab 360 mg flat dose every 3 weeks. As of 29 October 2018, 21 of 37 evaluable patients (56.8%) achieved a response by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

For select tumors, additional efficacy data have been presented. PIVOT-02 has a 2-stage design and data for either the Stage 1 (N1) population alone or in combination with the Stage 2 (N2; expansion) population were presented depending on data maturity. Data presented for the efficacy evaluable population (defined as having received one dose of study treatment and having undergone at least one scan) were as follows:

- In first-line RCC patients, a 46% (12 of 26 patients) ORR was observed (N = 48 enrolled; N = 26 in the N1 + N2 population; Diab 2018; 29 May 2018 cutoff).
- In first-line melanoma patients, a 53% (20 of 38 patients, including 35% [13 of 38] with complete response) ORR via blinded independent central review (BICR) was observed (N = 41 enrolled; N = 38 included in the N1 + N2 population; Diab 2019; 25 Sep 2019 data cutoff).
- In first-line metastatic urothelial carcinoma patients, a 48% (13 of 27 patients) ORR was observed (N = 41 enrolled; N = 27 in the efficacy evaluable population; Siefker-Radtke 2019; 03 Dec 2018 data cutoff).
- In metastatic triple-negative breast cancer (TNBC) patients, a 13% (5 of 38 patients) ORR was observed (N = 43 enrolled; N = 38 in the efficacy evaluable population; Tolaney 2019; 01 Jul 2019 data cutoff).

Additional details on the clinical experience with bempegaldesleukin are provided in the bempegaldesleukin Investigator's Brochure.

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

Serious events of cerebrovascular accident (CVA), including one fatal event, have been observed in patients who have received bempegaldesleukin in the triplet combination with nivolumab and ipilimumab, in the doublet combination with nivolumab, and in the combination of bempegaldesleukin, nivolumab, and other anticancer therapy. As of 28 October 2019, 3 of 43 patients (7.0%) who received triplet therapy in Study 16-214-02 had CVA events, including one fatal event; all of these CVA events were considered by the Investigator to be related to treatment with bempegaldesleukin, nivolumab, and ipilimumab. Additionally, 9 of 488 patients (1.8%) who received doublet therapy (bempegaldesleukin and nivolumab) had 10 CVA events, which were considered by the Investigator to be related to at least one of the study treatments in 4 patients (3 related to the doublet therapy and 1 related to nivolumab only); and one of 10 (10.0%) patients who received the combination of bempegaldesleukin, nivolumab, and other anticancer therapy (platinum-based chemotherapy) had a CVA event, which was considered by the Investigator to be unrelated to study treatment.

Although hypercoagulable state is a known confounder in cancer patients with solid tumors, based on these events and a comprehensive assessment of CVA across all bempegaldesleukin clinical studies, CVA has been escalated to an adverse event of special interest (AESI) for close monitoring and mitigations have been put in place for early identification and to reduce the incidence and/or risk of CVA. These mitigations include implementation of a cerebrovascular accident adverse event management algorithm (Appendix 2) and updates to the exclusion criteria, renal function and hydration assessment, hydration guidelines, concomitant and prohibited medications, dose modification guidelines, and discontinuation criteria.

Additional information on the clinical safety and risk of CVA is found in the bempegaldesleukin Investigator's Brochure.

2.1.3.2.3 Study 16-214-05 (PROPEL) Bempegaldesleukin and Pembrolizumab Combination Therapy

Study 16-214-05 is a Phase 1/2, open-label, multicenter study to investigate the safety and preliminary efficacy of bempegaldesleukin (0.006 mg/kg) in combination with atezolizumab (1200 mg q3w) or pembrolizumab (200 mg q3w) in patients with locally advanced or metastatic solid tumors, including HNSCC. Protocol Amendment 5.0 (dated 20 August 2019) ended enrollment to an atezolizumab arm.

As of 28 October 2019, 36 patients have been enrolled and have received at least 1 dose of study treatment. A total of 23 patients were enrolled in the bempegaldesleukin plus atezolizumab combination cohort and 13 patients have been enrolled in the bempegaldesleukin plus pembrolizumab combination cohort.

At least 1 treatment-related treatment-emergent AE (TEAE) was reported by 91.7% of patients (33 of 36 patients) overall, including 91.3% (21 of 23 patients) who received bempegaldesleukin plus atezolizumab and 92.3% (12 of 13 patients) who received bempegaldesleukin plus pembrolizumab. The most common treatment-related TEAEs were fatigue (19 of 36 patients, 52.8%), pyrexia (11 patients, 30.6%), nausea (10 patients, 27.8%), decreased appetite or vomiting (each 9 patients, 25.0%), and influenza-like illness (8 patients, 22.2%).

In the bempegaldesleukin plus atezolizumab cohort, the most frequently reported TEAEs assessed as related were fatigue (13 of 23 patients, 56.5%) pyrexia (8 of 23 patients, 34.8%), decreased appetite (7 of 23 patients, 30.4%), and influenza-like illness (5 of 23 patients, 21.7%).

In the bempegaldesleukin plus pembrolizumab cohort the most frequently reported TEAEs assessed as related were fatigue or nausea (each: 6 of 13 patients, 46.2%), vomiting (5 patients, 38.5%) and blood creatinine increased, chills, diarrhea, dizziness, dry mouth, influenza-like illness, myalgia, pruritus, pyrexia, or rash maculo-papular (each: 3 patients 23.1%).

Thirteen of the 36 patients (36.1%) experienced TEAEs ≥ Grade 3 assessed as related (7/23, 30.4% in the bempegaldesleukin plus atezolizumab group and 6/13, 46.2% in the

bempegaldesleukin plus pembrolizumab group). For each therapy cohort, all were single patient reports. Fatigue, anemia, arthralgia, or chills were reported by 2 patients each overall.

One Grade 5 TEAE was reported: cardiac arrest, not-related, in an 84-year-old, male patient with bladder cancer and prior cardiac illness in the bempegaldesleukin plus atezolizumab cohort. The patient died 5 days after the first dose of study drug. The patient's general condition was stated to be declining in the setting of disease progression.

2.2 Benefit/Risk Assessment

2.2.1 Bempegaldesleukin Safety Profile

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

Additional details on the clinical experience with bempegaldesleukin are provided in the bempegaldesleukin Investigator's Brochure.

2.2.2 Pembrolizumab Safety Profile

The safety profile of pembrolizumab in various approved indications is well established and consistent with other marketed check-point inhibitors. Extensive details on the safety profile of pembrolizumab are available in the pembrolizumab Investigator's Brochure.

The most common pembrolizumab adverse reactions (reported in ≥ 20% of patients) include pruritus, diarrhea, and cough. In the pembrolizumab monotherapy trials, the incidence of Grade 3-5 drug-related AEs across studies is 13.8%. Pembrolizumab immune-mediated AESIs are relatively uncommon. The most frequently reported AESI is hypothyroidism, with an overall incidence of 8.5%. Furthermore, most AESIs are mild to moderate in severity, and are generally readily manageable with appropriate care in the clinical setting.

In KEYNOTE-048, pembrolizumab monotherapy had a favorable safety profile compared with pembrolizumab with chemotherapy (ie, platinum and 5-fluorouracil) as first-line therapy for patients with recurrent or metastatic advanced HNSCC (Burtness 2019). Grade 3 or worse AEs occurred in 164 (55%) of 300 patients in the pembrolizumab monotherapy group and 235 (85%) of 276 in the pembrolizumab with chemotherapy group. AEs led to death in 25 (8%) patients in the pembrolizumab monotherapy group and 32 (12%) in the pembrolizumab with chemotherapy group. Pembrolizumab was discontinued for AEs in 12% of patients in the pembrolizumab monotherapy group and 16% of patients in the pembrolizumab with chemotherapy group; the most common AEs resulting in permanent discontinuation were (Merck 2020):

- Pembrolizumab monotherapy: sepsis (1.7%) and pneumonia (1.3%).
- Pembrolizumab with chemotherapy: pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%).

2.2.3 Bempegaldesleukin and Pembrolizumab Benefit and Risk Assessment

Advanced cancer patients in clinical trials generally cannot expect to receive direct benefit from pembrolizumab and bempegaldesleukin during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for patients participating in this clinical trial may be found in the accompanying pembrolizumab and bempegaldesleukin Investigator's Brochures and informed consent form (ICF) documents.

Pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications. Publications of a significantly positive benefit/risk ratio have been reported for melanoma in a single arm study encompassing nearly 1000 patients (KEYNOTE-001), which led to US Food and Drug Administration (FDA) approval in September 2014. Pembrolizumab subsequently received approval across a broad range of cancers, including for the treatment of patients with NSCLC and for the treatment of patients with recurrent or metastatic HNSCC. The pembrolizumab Investigator's Brochure provides additional details about these approvals. The US FDA approval to treat patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy was based on the favorable tumor response rate and durability of responses seen in KEYNOTE-012 and KEYNOTE-055. Finally, the Phase 3 KEYNOTE-048 study established pembrolizumab as an appropriate first-line treatment for patients with recurrent or metastatic HNSCC and tumors with PD-L1 CPS $\geq$ 1 (Burtness 2019). The potential benefits for patients with HNSCC are addressed in Section 2.1.2.2.

Bempegaldesleukin has been generally well-tolerated in the clinical studies to date, both as monotherapy as well as in combination with the PD-1 checkpoint inhibitor nivolumab, with promising evidence of clinical efficacy and a potentially favorable benefit-risk profile. Bempegaldesleukin has been safely administered in an outpatient setting supported by appropriate clinical monitoring.

Hypotension has been identified as a clinically significant adverse effect of bempegaldesleukin and can be effectively mitigated by prophylaxis and hydration guidelines. Other risks associated with bempegaldesleukin include cytokine-related toxicities (eg, flu-like symptoms, rash, pruritus, fatigue, hepatic transaminase elevations, and serum creatinine elevation), infusion-related reactions, thyroid dysfunction, eosinophilic disorder, and arthralgia; these AEs are generally mild or moderate in severity, and can be monitored and managed in the clinical setting. Cases of thyroid dysfunction (hypothyroidism, hyperthyroidism, thyroiditis), dermatitis, pneumonitis, hepatitis, myocarditis, myositis/myasthenia gravis, and vitiligo/hypopigmentation consistent with PD-L1/PD-1/CTLA-4 checkpoint immune-mediated mechanism have been observed in patients receiving bempegaldesleukin plus nivolumab; however, there is no evidence that bempegaldesleukin increases the frequency or severity of immune-mediated AEs (also referred to as immune-related AEs [irAEs] in this document) associated with nivolumab with the limitation of small sample size and relatively shorter treatment duration for bempegaldesleukin-treated patients.

The continued development of bempegaldesleukin in combination with PD-1 checkpoint inhibitors such as pembrolizumab for the treatment of various cancers is warranted based on a positive benefit-risk profile. In addition, the early efficacy data along with the correlative biomarker showing conversion of PD-L1 negative patients to PD-L1 positive patients suggests that the addition of bempegaldesleukin to a PD-1/PD-L1 checkpoint inhibitor may change the tumor microenvironment in PD-L1 negative patients such that the combination therapy may contribute to enhanced anti-tumor activity with an acceptable safety profile. Preliminary data from the PIVOT-02 study in the metastatic melanoma setting have suggested that this combination may improve upon the treatment effects of the checkpoint inhibitor nivolumab alone. The combination of bempegaldesleukin and nivolumab led to an ORR of 53% by independent radiology review, which included a 34% complete response (CR) rate (Diab 2019), and these data were the basis for the FDA granting a breakthrough therapy designation for the treatment of patients with previously untreated unresectable or metastatic melanoma. A Phase 3 randomized clinical trial of bempegaldesleukin in combination with nivolumab versus nivolumab alone in patients with previously untreated unresectable or metastatic melanoma is ongoing (NCT03635983).

2.2.4 Data Monitoring Committee

The study will use an independent, external Data Monitoring Committee (DMC) to monitor efficacy and safety. Safety will be evaluated by the DMC approximately twice a year. There will be 2 interim analyses evaluated by the DMC. The first interim futility analysis will occur at least one month after the last patient of the Phase 2 portion has been randomized into the study. The second interim efficacy analysis will be conducted when approximately 500 patients have been randomized and about 231 OS events have been observed. The DMC will also meet on an ad-hoc basis if needed (see Section 11.8).

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

This is a multicenter, randomized, open-label, Phase 2/3 study that will evaluate the efficacy and safety of bempegaldesleukin combined with pembrolizumab compared with pembrolizumab monotherapy in patients with recurrent or metastatic HNSCC with positive PD-L1 expression (CPS ≥ 1).

The study will use an adaptive design based on prespecified criteria and an independent, external Data Monitoring Committee (DMC) to monitor efficacy and safety. Safety will be evaluated by the DMC approximately twice a year. The first interim analysis will address futility. Enrollment will pause for approximately 4 months after approximately 200 patients have been randomized, and the first interim analysis will occur at least one month after the last patient of the Phase 2 portion has been randomized into the study. If the ORR passes the prespecified futility boundary, the Phase 3 portion of the study will begin with an expected 300 additional patients to be randomized. The second interim analysis will be conducted when approximately 500 patients have been randomized and about 231 overall survival events have been observed. At the second interim analysis, if the OS efficacy boundary is crossed, the trial will be stopped for efficacy. Otherwise, conditional power will be calculated to determine the overall survival event size for final analysis.

Patients will be randomized at a 1:1 ratio to receive one of two treatments:

- Arm A: Bempegaldesleukin plus pembrolizumab every 3 weeks (q3w) for up to 35 cycles (approximately 2 years).
- Arm B: Pembrolizumab monotherapy q3w for up to 35 cycles (approximately 2 years).

Randomization will be stratified according to the following factors:

1. Disease status (metastatic vs recurrent only).
2. PD-L1 tumor expression determined by a local or the central laboratory using the PD-L1 IHC 22C3 PharmDx diagnostic kit (CPS ≥ 20 vs CPS 1-19).

   Note: CPS is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen should be considered to have PD-L1 expression if CPS ≥ 1.
3. Human papillomavirus (HPV) status for oropharyngeal cancer determined by p16 IHC (positive vs negative). For patients with cancers of the oral cavity, hypopharynx, and larynx, HPV status is considered HPV negative.

The Sponsor estimates that the study will be fully enrolled within approximately 25 months. Analyses are anticipated at the following times (relative to the first patient's randomization date): approximately 14 months for the first interim analysis, approximately 32 months for the second interim analysis, and approximately 38 to 52 months for the final analysis for OS.

Section 1.1 provides the study schematic and Section 1.2 provides the Schedule of Events.

3.2 Rationale for Study Design

3.2.1 Open-Label Design

The study will have an open-label design with a BICR. There are multiple reasons that would make blinding the trial impractical or impossible:

1. The hydration guidelines, which only apply to patients in Arm A (bempegaldesleukin plus pembrolizumab).
2. The withholding of anti-hypertensive medications, which only applies to patients in Arm A (bempegaldesleukin plus pembrolizumab).
3. The unique adverse event profile of bempegaldesleukin may easily unblind the patient study drug assignment.

Therefore, a placebo-controlled, double-blinded design is not appropriate for this study.

3.2.2 Choice of Endpoints

3.2.2.1 Primary Endpoints

Overall survival is the gold standard endpoint to demonstrate efficacy of antineoplastic therapy.

ORR per RECIST 1.1 criteria as assessed by blinded independent central radiology review will serve as an additional measure of efficacy. RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Because the treatment assignment is unblinded, images will be read by independent radiologists blinded to treatment assignment to minimize bias in the response assessments. In addition, final determination of radiologic progression will be based on the central assessment of progression, rather than site assessment. Real-time determination of radiologic progression as determined by central review will be communicated to the site.

3.2.2.2 Safety

Assessment of safety will be determined by an ongoing review throughout the study of treatment-emergent AEs, including treatment-related AEs, SAEs, AESIs, and AEs leading to drug discontinuation, clinical laboratory tests, and vital signs. All AEs will be assessed for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 guidelines.

3.2.3 Prospective Stratification

Randomization will be stratified by 3 factors:

- Disease status (metastatic vs recurrent only). In the KEYNOTE-048 trial, metastatic versus recurrent only disease status demonstrated a prognostic value for patient survival (Burtness 2019).
- PD-L1 tumor expression determined by PD-L1 IHC (CPS ≥ 20 vs CPS 1-19). The KEYNOTE-048 trial demonstrated a statistically significant improvement in OS in the subgroup of patients with CPS ≥ 1 randomized to single-agent pembrolizumab. The median OS for CPS ≥ 1 in months was 12.3 (95% CI: 10.8, 14.9). The median OS for the CPS ≥ 20 subgroup in months was 14.9 (95% CI: 11.6, 21.5) for single agent pembrolizumab (Burtness 2019). In an exploratory subgroup analysis, CPS 1 – 19 median OS was 10.8 months (95% 9.0, 12.6) for single agent pembrolizumab (Merck 2020).
- HPV status (positive or negative) for patients with head and neck cancer of the oropharynx. The favorable prognostic significance of HPV-positive head and neck cancers in the oropharynx has been increasingly established (Fakhry 2008). Preliminary data of single agent pembrolizumab in head and neck cancer patients in KEYNOTE-012 demonstrate efficacy in both HPV-positive and HPV-negative patients. Investigator site assessment of HPV using IHC staining for the p16 protein will be used for the patients with oropharyngeal cancer prior to randomization.

3.2.4 Duration of Treatment with Bempegaldesleukin/Pembrolizumab

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. Study CA209003 (NCT00730639), a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 patients with NSCLC), specified a maximum treatment duration of 2 years. Among 16 patients with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 patients were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years (Brahmer 2017). These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and nonsquamous NSCLC respectively) (Felip 2017).

Similar results have been reported in clinical studies of pembrolizumab. KEYNOTE-010 (NCT01905657) was a randomized Phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in patients with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR = 0.72, p-value = 0.00017) and pembrolizumab 10 mg/kg (HR = 0.60, p-value < 0.00001) compared to docetaxel, with an

OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years (Herbst 2016).

KEYNOTE-006 (NCT01866319) was a randomized Phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2-year duration of pembrolizumab treatment. A total of 104 (19%) of 556 patients randomized to pembrolizumab completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients (Robert 2017).

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

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153 (NCT02066636), patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared with those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateaued approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years (Spigel 2017).

Collectively, these data suggest that there is minimal if any benefit derived from continuing immune-oncology treatment beyond 2 years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, the initial treatment will be given for a maximum of 35 cycles (approximately 2 years) following the date of the first dose of study drug.

Given the hypothesis that co-administration of bempegaldesleukin with pembrolizumab will potentiate the pharmacological effects of pembrolizumab, the duration of bempegaldesleukin therapy will also be restricted to 35 cycles (approximately 2 years) to match the duration of pembrolizumab therapy.

3.2.5 Justification for Dose

3.2.5.1 Bempegaldesleukin

Bempegaldesleukin 0.006 mg/kg q3w was chosen as the RP2D in the PIVOT-02 study based on the observed clinical safety profile as well as the clinical evidence of a robust immune system activation. Refer to Section 2.1.3.2.2 for additional details regarding the PIVOT-02 study.

3.2.5.2 Pembrolizumab

Pembrolizumab will be given at 200 mg q3w IV according to the label. Based on the totality of data generated in the pembrolizumab development program, 200 mg q3w is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg q3w to 10 mg/kg every 2 weeks (q2w).
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg q3w across multiple indications.
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based PK analysis) at 200 mg q3w.

Among the 8 randomized dose-comparison studies, a total of 2262 patients were enrolled with melanoma and NSCLC, covering different disease settings (treatment naive, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg q3w versus 10 mg/kg q3w (KEYNOTE-001 B2, KEYNOTE-001 D, KEYNOTE-002, KEYNOTE-010, and KEYNOTE-021), and three studies compared 10 mg/kg q3w versus 10 mg/kg q2w (KEYNOTE-001 B3, KEYNOTE-001 F2, and KEYNOTE-006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) q3w provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg q3w as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg q3w. First, PK data in KEYNOTE-001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg q3w. Secondly, a physiologically based PK analysis was conducted to predict tumor PD-1 saturation over a wide

range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg q3w achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other patient covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg q3w fixed dose and 2 mg/kg q3w dose. Supported by these PK characteristics, and given that a fixed dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg q3w fixed-dose was selected for evaluation across all pembrolizumab protocols.

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

3.2.5.3 Rationale for Bempegaldesleukin/Pembrolizumab Combination

Accumulating evidence suggests that patients with low baseline CD8+ T cells within the tumor microenvironment (tumor infiltrating lymphocytes [TILs]) predict poor response to checkpoint inhibitor immunotherapies (Daud 2016a; Daud 2016b); thus, agents designed to specifically activate and expand CD8+ T cells may improve clinical outcomes in patients with low TILs. NKTR-214 targets the IL-2 pathway and is designed to provide biased sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rβγ) to preferentially activate NK and effector CD8+ T cells over Treg cells. Preliminary analyses of patients' blood and tumor by flow cytometry and IHC demonstrate that NKTR-214, as a single agent, increases activated CD4+ and CD8+ T cells in peripheral blood, with an increase in T-cell infiltrates within the tumor tissue after 1 dose of NKTR-214. In addition, there is an increase in programmed cell death receptor-1 (PD-1) expression on T cells in the blood and tumor after treatment with NKTR-214. The ability to alter the immune environment and increase PD-1 expression on effector T cells may improve the effectiveness of anti-PD-1/anti-PD-L1 blockade.

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objectives and Endpoints

In patients who are aged 18 years and older with recurrent or metastatic HNSCC and positive PD-L1 expression (CPS ≥ 1) who have not received prior therapy for the treatment of recurrent or metastatic HNSCC, the primary objectives and endpoints are:

Primary Objective	Endpoint
To compare the overall survival (OS) of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy.	OS, defined as the time from randomization to death due to any cause.
To compare the objective response rate (ORR) of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy.	ORR, defined as the rate of confirmed complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by blinded independent central review (BICR).

4.2 Secondary Objectives and Endpoints

The secondary objectives and endpoints listed below involve comparison of bempegaldesleukin plus pembrolizumab versus pembrolizumab monotherapy in first-line patients with recurrent or metastatic HNSCC and positive PD-L1 expression (defined by CPS ≥ 1) who have not received prior therapy for the treatment of recurrent or metastatic HNSCC:

Secondary Objective	Endpoint
To compare progression-free survival (PFS).	PFS, defined as the time from randomization to the first documented disease progression (per RECIST 1.1 by BICR) or death due to any cause, whichever occurs first.
To compare time to deterioration in global health status/quality of life, pain, and swallowing.	The time from baseline to a ≥ 10-point decrease from baseline with confirmation by the subsequent visit of a ≥ 10-point deterioration from baseline in: • Global health status/quality of life assessment based on the global health status/quality of life scales of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30). • Pain based on the pain multi-item scales of EORTC QLQ head and neck cancer specific module (EORTC QLQ-H&N35). • Swallowing based on the swallowing multi-item scales of EORTC QLQ-H&N35.
To compare mean change from baseline in global health status/quality of life.	Mean change from baseline in global health status/quality of life scales of EORTC QLQ-C30.
To compare the overall safety and tolerability.	Safety will be based on assessments of treatment-emergent adverse events (AEs) and serious AEs (SAEs).

[redacted]

5.0 SELECTION OF STUDY POPULATION

5.1 Inclusion Criteria

An eligible patient must meet all of the following criteria:

1. Provide written, informed consent to participate in the study and follow the study procedures. The Investigator takes responsibility for ensuring that all vulnerable patients are protected and participate voluntarily in an environment free from coercion or undue influence. The patient may also provide consent for additional research (described in Section 8.3.3). However, the patient may participate in the study without participating in additional research.
2. Male or female patients, age 18 years or older at the time of signing the informed consent form (ICF).
3. Have histologically or cytologically-confirmed recurrent or metastatic HNSCC that is considered incurable by local therapies.
    a. No prior systemic therapy for recurrent or metastatic disease. Systemic therapy given as part of multimodal treatment for locally advanced disease is allowed if completed more than 6 months prior to signing consent.
    b. The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.
    c. Patients may not have a primary tumor site of nasopharynx (any histology) and/or unknown primary.
4. Have measurable disease based on RECIST 1.1 as determined by the local site Investigator. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions since irradiation.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 3).
6. Provide tumor tissue from a core, incisional, or excisional biopsy (fine needle aspirates are not acceptable) to the central laboratory for determination of PD-L1 status (if not determined at local laboratory) [redacted]. Repeat samples may be required if adequate tissue is not provided for assessment of PD-L1 status. A newly obtained biopsy is strongly preferred, but archival tumor biopsy may be used and provided (see Section 8.3.1).
7. The tumor must have positive PD-L1 expression (ie, CPS $\geq$ 1) as determined by a local or the central laboratory with the IHC 22C3 PharmDx diagnostic kit.

8. Patients with oropharyngeal cancer: must have results from testing of HPV status defined as p16 IHC testing using CINtec® p16 Histology assay. If HPV status was previously tested using this method, no additional testing is required. Note:

   a. Tumor p16 expression must be evaluated by assessment of IHC analysis with CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ) using 'Benchmark Ultra' autostainer (Ventana, Tucson, AZ) and standard protocol. Positive p16 expression is defined as strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells.

   b. If local p16 testing results are not available, or cannot be assessed by the specified method, a tumor tissue sample may be submitted to the central laboratory for p16 testing.

   Patients with oral cavity, hypopharynx, or larynx cancers: HPV testing by p16 IHC is not required as by convention these tumor locations are assumed to be HPV negative.

9. Demonstrated adequate organ function as defined below (see Section 10.18 for clinical laboratory test information):

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1500/μL (1.5×10^9/L) without myeloid growth factor support for 7 days preceding the lab assessment
Platelets	Platelet count ≥ 100,000/μL (100×10^9/L) without platelet transfusions for 7 days preceding the lab assessment
Hemoglobin	Hemoglobin ≥ 9.0 g/dL (90 g/L) without erythropoietin-stimulating agents or transfusion for 14 days preceding the lab assessment
Renal	
Serum creatinine **OR** measured or calculated creatinine clearance[a] (GFR can also be used in place of creatinine or creatinine clearance)	≤ 1.5 × ULN **OR** ≥ 60 mL/min for patients with creatinine levels > 1.5 × ULN
Hepatic	
Total bilirubin	≤ 1.5 × ULN **OR** Direct bilirubin ≤ ULN for patients with total bilirubin > 1.5 × ULN
AST or ALT	≤ 2.5 × ULN
Digestive	
Lipase and amylase	≤ 1.5 × ULN Patients with pancreatic metastases and lipase and/or amylase < 3× ULN may enroll. Patients may not enroll if there are clinical or radiographic signs of pancreatitis.
Coagulation	
INR or PT aPTT	≤ 1.5 × ULN unless the patient is receiving anticoagulant therapy, as long as PT or aPTT is within the therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT) = alanine transaminase (serum glutamic pyruvic transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate transaminase (serum glutamic oxaloacetic transaminase); GFR = glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; ULN = upper limit of normal

a. Creatinine clearance should be calculated according to institutional standard.

10. A documented left ventricular ejection fraction (LVEF) > 45% using standard echocardiogram or multigated acquisition (MUGA) scan test.
11. Patients with hypertension must be on a stable antihypertensive regimen for the 14 days prior to the first dose of study drug. Need for ≤ 2 antihypertensive medications for management of hypertension (including diuretics) permitted (for patients randomized to Arm A receiving bempegaldesleukin: Section 6.7.2.2 provides additional on-treatment considerations regarding antihypertensive medications).
12. Oxygen saturation ≥ 90% on room air.
13. Clinically significant toxic effect(s) of the most recent prior anticancer therapy must be Grade 1 or resolved (except alopecia, neuropathy, adrenal insufficiency and hypothyroidism). Note:
    a. Patients with ≤ Grade 2 neuropathy are eligible.
    b. Patients with endocrine-related AEs Grade ≤ 2 requiring treatment or hormone replacement may be eligible. Specifically, patients with Grade ≤ 2 adrenal insufficiency (defined as requiring medical intervention, such as concomitant steroids) or Grade ≤ 2 hypothyroidism (defined as requiring hormone replacement therapy) may be enrolled provided that clinical symptoms are adequately controlled and the daily dose is 10 mg or less of prednisone or equivalent.
    c. If the patient had a major operation, the patient must have recovered adequately from the procedure and/or any complications from the operation before starting study intervention.
14. Reproductive Status
    a. Women of childbearing potential (WOCBP) must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for urine or within 72 hours for serum before the first dose of study treatment.
    Note: If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the patient must be excluded from participation if the serum pregnancy result is positive.
    b. Women must not be breastfeeding.
    c. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment and for at least 120 days after the last dose of study treatment or 30 days after cessation of study drug if the patient initiates a new anticancer treatment. Women should use an adequate method(s) of contraception as indicated in Appendix 5. WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this protocol.

Note: The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

d. For Arm A: Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) and at least 3 months after the last dose of bempegaldesleukin. In addition, male patients must be willing to refrain from sperm donation during this time (Appendix 5).

   For Arm B: For males receiving pembrolizumab monotherapy, there are no contraception requirements.

15. Patients who are hepatitis B surface antigen (HBsAg) positive are eligible if they have received hepatitis B virus (HBV) antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to randomization.
    Note: Patients should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention. Hepatitis B screening tests are not required unless:
    - Known history of HBV infection
    - As mandated by local health authority

16. Patients with history of hepatitis C virus (HCV) infection are eligible if HCV viral load is undetectable at screening.
    Note: Patients must have completed curative antiviral therapy at least 4 weeks prior to randomization. Hepatitis C screening tests are not required unless:
    - Known history of HCV infection
    - As mandated by local health authority

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

5.2 Exclusion Criteria

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

1. Has disease that is suitable for local therapy administered with curative intent.
2. Has progressive disease within 6 months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC.

3. Has had radiation therapy (or other non-systemic therapy) within 2 weeks prior to initiation of study drug, or patient has not fully recovered (ie, ≤ Grade 1 or at baseline) from AEs due to a previously administered treatment. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-central nervous system (CNS) disease. Note:
    a. Patients with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and qualify for the study.
    b. If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
4. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) as determined by the Investigator.
5. Has a known additional malignancy that is progressing or has required active treatment within 5 years prior to the first dose of study drug with the exception of: curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, curatively resected in situ cervical cancer, and curatively resected in situ breast cancer.
6. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
7. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. Corticosteroid use as pre-medication for allergic reactions (eg, IV contrast) is allowed. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
8. Use of an investigational agent or an investigational device within 28 days before the first dose of study drug.
    Note: Patients who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
9. Prior treatment with an anti PD-1, anti PD-L1, anti-PD-L2, or anti CTLA-4 antibody, agents that target IL-2 pathway, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways.

10. Has known active CNS metastases and/or carcinomatous meningitis.
    Note: Patients with previously treated brain metastases may participate provided they are radiographically stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either magnetic resonance imaging (MRI) or computed tomography (CT) scan] for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
11. History of severe hypersensitivity (≥ Grade 3) to study drug components (for pembrolizumab, bempegaldesleukin, or any of their excipients).
12. History of severe hypersensitivity reaction to any monoclonal antibody.
13. History of allogeneic tissue/solid organ transplant.
14. Uncontrolled tumor-related pain. Patients requiring narcotic pain medication must be on a stable regimen at study entry. Symptomatic lesions (eg, bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to the first dose of study drug. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.
15. Active infection requiring systemic therapy.
16. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
17. Has concurrent active hepatitis B (defined as HBsAg positive and/or detectable HBV deoxyribonucleic acid [DNA]) and hepatitis C virus (defined as anti-HCV antibody positive and detectable HCV ribonucleic acid [RNA]) infection.
    Note: Hepatitis B and C screening tests are not required unless:
    - Known history of HBV and HCV infection
    - As mandated by local health authority
18. Known history of positive test for human immunodeficiency virus (HIV 1/2 antibodies).
19. Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study within 2 weeks prior to the first dose of study drug. Refer to Section 6.7.2 for prohibited concomitant medications.
20. Prolonged Fridericia's corrected QT interval (QTcF) > 450 msec for men and > 470 msec for women at Screening.
21. Known cardiovascular history, including unstable or deteriorating cardiac disease, within the previous 12 months prior to the first dose of study drug including, but not limited to, the following:
    a. Unstable angina or myocardial infarction.

b. Transient ischemic attack (TIA)/Cerebrovascular accident (CVA).

c. Congestive heart failure (New York Heart Association [NYHA] Class III or IV).

d. Uncontrolled clinically significant arrhythmias.

22. Need for > 2 antihypertensive medications for management of hypertension (including diuretics). Patients with hypertension must be on a stable antihypertensive regimen (defined as no dose adjustments to antihypertensive medications) for the 14 days prior to the first dose of study drug.
Note: An antihypertensive medication that contains 2 drugs under one formulation is counted as 2 antihypertensive medications (eg, angiotensin-converting-enzyme [ACE] inhibitor plus diuretic, calcium channel blocker plus ACE inhibitor).

23. History of pulmonary embolism, deep vein thrombosis (DVT), or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event within 3 months prior to the first dose of study drug.

- Patients with a history of a venous or arterial thromboembolic event must be asymptomatic for at least 2 weeks prior to enrollment and must be receiving a stable regimen of therapeutic anticoagulation (preferably low molecular weight heparin [LMWH] or direct oral anticoagulants [DOAC]; see Section 6.7.3.3). Note: unless there is a new medical contraindication observed after Cycle 1 Day 1, a patient with a history of venous or arterial thromboembolic event must be willing to maintain therapeutic anticoagulation throughout participation in the treatment phase of the study.

24. Patients who have received a live / attenuated vaccine within 30 days of the first dose of study drug. Note: Killed vaccines are allowed.

25. Any contraindication or exclusions specific to pembrolizumab included in the current package insert, Summary of Product Characteristics, or the applicable country-specific prescribing guidelines.

26. Any condition including medical, emotional, psychiatric, substance abuse, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results (eg, a condition associated with diarrhea or acute diverticulitis).

6.0 TREATMENT PLAN

6.1 Screening Period

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

Furthermore, additional evaluations/testing may be deemed necessary by the Investigator and/or the Sponsor for reasons related to patient safety. In some cases, such evaluations/testing may be potentially sensitive in nature (eg, HIV, hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the patient. In these cases, such evaluations/testing will be performed in accordance with those regulations.

6.1.1 Screening Failure

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

Re-screening will be allowed for a patient who has discontinued the study as a pretreatment failure (ie, patient has not been randomized). Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met. If re-enrolled, the patient must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single Screening period will be permitted (in addition to any parameters that require a confirmatory value). The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the patient's most current clinical state.

Laboratory parameters and/or assessments that are included in the Schedule of Events (Section 1.2) may be repeated in an effort to find all possible well-qualified patients. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

6.2 Treatment Period

Section 1.2 provides the study assessments to be performed during the treatment period. 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, the

coronavirus disease 2019 (COVID-19) public health emergency, or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation and should be documented as described in Section 13.1.

The duration of study treatment is described in Section 6.2.4.

Patients with progressive disease per RECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator; see Section 6.2.5 for treatment beyond progression. Patients with a partial response (PR) or with stable disease will continue to receive study drugs until disease progression, or intolerability to therapy. It is at the discretion of the Investigator to continue treating patients with a confirmed CR for a maximum treatment of 35 cycles (approximately 2 years).

6.2.1 Treatment Assignment and Patient Number Assignment

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

An Interactive Response Technology (IRT) will be employed to manage patient randomization and drug supply.

Following Screening and confirmation of a patient's eligibility, patients will be randomized in a 1:1 ratio to Arm A (bempegaldesleukin in combination with pembrolizumab) or Arm B (pembrolizumab monotherapy) using the IRT system. Within 5 calendar days following randomization, the patient should receive the first dose of study treatment.

6.2.2 Administration of Study Drugs

Table 3 provides the timing of study drug administration. Dosing visits are not skipped, only delayed.

Study agent(s) should be administered in an area with access to resuscitation equipment.

Table 3: Selection and Timing of Dose

Study Treatment	Starting dose	Frequency of Administration	Route of Administration
Bempegaldesleukin (NKTR-214)[a]	0.006 mg/kg	q3w	IV
Pembrolizumab	200 mg	q3w	IV

Abbreviations: IV = intravenous; q3w = every 3 weeks

a. Bempegaldesleukin dose is based on IL-2 content.

6.2.2.1 Arm A: Bempegaldesleukin Dosing

Patients should be carefully monitored for infusion reactions during bempegaldesleukin administration. If an acute infusion reaction is noted, patients should be managed according to Section 6.5.1.1.1. If the patient experiences a Grade ≥ 2 infusion-related reaction or hypotension during the days after bempegaldesleukin dosing, the patient may be monitored overnight at the discretion of the Investigator; longer periods of monitoring may be implemented at the discretion of the Investigator.

Treatment with bempegaldesleukin may be delayed or reduced as described in Section 6.5.1.2. No dose escalations of bempegaldesleukin above 0.006 mg/kg are allowed (see Section 6.5.1.2 for information regarding patients with a bempegaldesleukin dose reduction). Bempegaldesleukin monotherapy may continue if pembrolizumab is permanently discontinued due to toxicities.

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

6.2.2.2 Arm A and Arm B: Pembrolizumab Dosing

Pembrolizumab dosing will be as follows:

- **Arm A**: Patients in Arm A should receive pembrolizumab at least 30 minutes after the end of the bempegaldesleukin infusion. Do not co-administer pembrolizumab with the same IV line used for bempegaldesleukin; the pembrolizumab infusion must be administered using a separate infusion set with an in-line filter, which include add-on filters (also known as an in-line filter extension set). Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion on Day 1 of each treatment cycle q3w (± 3 days). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between −5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes −5 min/+10 min).
- **Arm B**: Patients in Arm B will receive pembrolizumab as a dose of 200 mg using a 30-minute IV infusion on Day 1 of each treatment cycle q3w (± 3 days). The pembrolizumab infusion must be administered using an infusion set with an in-line filter, which include add-on filters (also known as an in-line filter extension set). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between −5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes −5 min/+10 min).

No dose escalations or reductions of pembrolizumab are allowed. Patients may be dosed no less than 18 days from the previous dose during q3w cycles.

Patients should be carefully monitored for infusion reactions during pembrolizumab administration. If an acute infusion reaction is noted, patients should be managed according to the directions in Section 6.5.2.1.1.

Doses of pembrolizumab may be interrupted, delayed, or discontinued depending on how well the patient tolerates the treatment (see Section 6.5.2.1). Pembrolizumab monotherapy may continue if bempegaldesleukin is permanently discontinued due to toxicities.

Flush the IV line with an appropriate amount of diluent to ensure that the total dose is completely administered over the appropriate time. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

6.2.3 Monitoring, Vital Signs, and Hydration Guidelines

The study site must be equipped for medical emergencies.

6.2.3.1 Frequent Vital Signs

Refer to Section 10.20 for vital sign measurements, which are to be monitored according to the Schedule of Events (Section 1.2).

6.2.3.2 Arm A: Hydration Guidelines

Important safety information and hydration instructions are to be provided to patients in Arm A receiving bempegaldesleukin and pembrolizumab. Hydration and renal function should be assessed within 24 hours prior to study drug administration or as soon as locally feasible (see Appendix 1B for the list of local laboratory tests that require evaluation prior to bempegaldesleukin administration). Underlying reasons for decreased oral intake (such as nausea) should be addressed and treatment (such as IV hydration) should be provided. Patients may receive additional hydration precautions in a patient card.

For those patients receiving bempegaldesleukin and pembrolizumab, administer at least 1 liter of IV fluid on bempegaldesleukin dosing days (at any time on Day 1 of each cycle). For the next 3 days (Days 2-4) after administration of bempegaldesleukin, patients are to be instructed to drink at least 2 liters per day (ie, 8–10 glasses) of self-administered oral hydration. Advise patients to avoid activity that may contribute to dehydration (including, but not limited to, strenuous activity, long hot showers, and saunas) for Days 1 to 4 of each cycle of bempegaldesleukin treatment. Advise patients with orthostatic symptoms to call their treating oncologist and consider increasing oral hydration.

In Cycles 1 and 2, site personnel must contact the patient (by telephone or clinic visit) once between Days 3 and 5 (inclusive) following infusion, to remind the patient of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion (Section 1.2). Following subsequent bempegaldesleukin administrations, the oral hydration follow-up should be conducted as clinically indicated for patients receiving bempegaldesleukin.

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

6.2.4 Duration of Treatment

In the initial treatment (ie, First Course), patients may remain on treatment for up to 35 cycles (approximately 2 years) of study drug (ie, bempegaldesleukin plus pembrolizumab or pembrolizumab monotherapy). Note: the number of cycles of study medication is calculated starting with the first dose.

For patients who have attained a confirmed complete response and have received at least 2 cycles of study drug beyond the initial complete response confirmation date, treatment may be stopped.

These patients may be eligible for the Second Course as described in Section 6.2.6.

6.2.5 Treatment Beyond Progression

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (Wolchok 2009; Nishino 2015). Patients will be permitted to continue assigned study drug beyond initial RECIST 1.1-defined progressive disease (confirmed by BICR) up to a maximum of 35 cycles (approximately 2 years) from the date of first study drug dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit.
- Patient tolerates study treatment.
- Stable ECOG performance status.
- Absence of signs and symptoms indicating clinical disease progression (eg, increased pain or worsening laboratory values).
- Absence of tumor progression at critical anatomical sites (eg, brain metastases or cord compression) requiring urgent intervention.
- Patient provides written informed consent prior to receiving additional study treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

Radiographic assessment/scan(s) should continue in accordance with the Schedule of Events (Section 1.2) for the duration of the treatment beyond progression and should be submitted to the central imaging vendor.

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

6.2.6 Second Course Phase

All patients who have stable disease, partial response, or complete response may be eligible for up to an additional 17 cycles (approximately 1 year) of study treatment if there is Investigator-determined radiographic disease progression by RECIST 1.1 after the initial treatment (ie, First Course) has been completed or stopped for confirmed CR as specified in Section 6.2.4. This retreatment is the Second Course of this study. Patients who restart treatment will be retreated with the same study drug(s) and at the same dose as when they last received study drug.

Patients may enter the Second Course if all of the following criteria are met:

1. No new anticancer treatment was administered after the last dose of study intervention.
2. The patient meets all of the inclusion criteria and none of the exclusion criteria (see Section 5.0). Initial screening results are acceptable and do not need to be repeated for the Second Course for the following Section 5.1 inclusion criteria 3a, 6, 7, 8, 10, 15, and 16 and the following in Section 5.2 exclusion criteria 2, 9, 17, 18, and 20.
3. The study is ongoing.

An objective response or disease progression that occurs during the Second Course will not be counted as an event for the primary analysis of either endpoint in this study.

Visit requirements for the Second Course Phase are outlined in Section 1.2, Second Course Phase – Retreatment with Study Drug.

6.2.7 Lost to Follow-Up

If a patient fails to return to the clinic for a required study visit and/or if the site is unable to contact the patient, the following procedures are to be performed:

- The site must attempt to contact the patient and reschedule the missed visit. If the patient is contacted, the patient should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The Investigator or designee must make every effort to regain contact with the patient at each missed visit (eg, telephone calls and/or a certified letter to the patient's last known mailing address or locally equivalent methods). These contact attempts should be documented in the patient's medical record.

Note: A patient is not considered lost to follow-up until the last scheduled visit for the individual patient. The missing data for the patient will be managed via the prespecified statistical data handling and analysis guidelines.

6.3 Long-Term Follow-Up

Section 1.2 presents the long-term follow-up assessments.

6.3.1 Follow-Up Visits

Both Follow-Up Visits should be conducted in person and should occur regardless of initiation of subsequent anticancer therapy as follows:

- Follow-Up Visit 1 should occur 30 (± 7) days from the last dose of all study drug(s) or before a new antineoplastic regimen starts
- Follow-Up Visit 2 occurs 90 (± 7) days from the last dose of all study drug(s).

If the patient is unable to return to the clinic (eg, due to the COVID-19 public health emergency) for Follow-Up Visits, assessments and laboratory samples may be collected by research staff or designee at an alternate location or by phone as necessary; the location of the protocol-mandated visit (eg, real-time video conference) should be documented as described in Section 13.1.

Per clinical judgment, the patient may come in earlier for additional follow up.

Patients will also be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drugs (bempegaldesleukin and/or pembrolizumab) as outlined in Sections 10.5 and 10.8.

For AE and SAE reporting periods, please refer to Sections 10.5 and 10.7.

6.3.2 Survival Follow-Up

All patients will be contacted for survival every 12 weeks (± 14 days) following Follow-Up Visit 2 (or following last contact with the patient, if Follow-Up Visit 2 is missed) as follows:

- Survival visits may be conducted in person or by telephone.
- The Sponsor may request that survival data be collected on all treated patients outside of the scheduled contacts. At the time of this request, each patient will be contacted to determine their survival status unless the patient has withdrawn consent for all contact or is lost to follow-up (as defined in Section 6.2.7). Alternative methods to determine survival status may be used (eg, access to medical records and public record searches) as allowed by local regulations and/or guidelines.
- For patients who discontinue study treatment before BICR-confirmed disease progression, radiographic tumor assessments will continue to be collected every 6 weeks (± 7 days) or more frequently if clinically indicated. One year after randomization, radiographic tumor assessments will continue to be collected every 9 weeks (± 14 days) until BICR-confirmed disease progression, patient withdraws consent, death, initiation of subsequent anticancer therapy, or study termination by the Sponsor.

- Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after next line of therapy will be collected.
- Survival follow up should continue until patient withdrawal of consent for survival follow-up, death, loss to follow-up, or study termination by the Sponsor.

6.4 End of Study

End of study is defined as no more than 5 years after the last patient received their first dose of study drug or Sponsor decision to terminate the study, whichever comes first.

6.5 Dose Modification and Management of Specific Adverse Events

Every effort should be made to follow planned dosing schedules for all study drugs in both treatment arms. Study drug administration may be delayed or modified for toxicity as described below and must be discontinued as required by criteria described in Section 6.6.

For patients in Arm A (bempegaldesleukin plus pembrolizumab): Dose modification for bempegaldesleukin in Arm A may be considered independently from pembrolizumab based on Investigator assessment of relationship of a toxicity to each of the study drugs. If only one of the study drugs meets the criteria for dose delay, then administration of the other study drug may be continued or delayed at the discretion of the Investigator. Likewise, in the event that one of the study drugs in Arm A is permanently discontinued due to toxicities, the other can continue to be administered.

Patients who require a dose delay of pembrolizumab or bempegaldesleukin should be re-evaluated weekly or more frequently if clinically indicated and should resume treatment with combination of bempegaldesleukin and pembrolizumab when retreatment criteria are met. Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

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

6.5.1 Bempegaldesleukin

6.5.1.1 Monitoring and Management of Specific Adverse Events

6.5.1.1.1 Infusion Reactions

Infusion reactions have been reported during infusions with bempegaldesleukin. If such a reaction were to occur with the bempegaldesleukin infusion, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions.

Dose modification and toxicity management guidelines for bempegaldesleukin infusions should follow those provided for pembrolizumab infusion reactions that are provided in Table 5 (Section 6.5.2.1.1). For patients randomized to Arm A receiving bempegaldesleukin, note:

- In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).
- If a patient has experienced a previous infusion reaction to bempegaldesleukin, subsequent doses of bempegaldesleukin may be administered at a reduced rate (over longer duration) per Investigator discretion (eg, 50% of the initial rate of infusion). The investigator may also consider re-elevating the rate of infusion if the patient tolerates the subsequent dose(s) well. The Investigator may consult with the Medical Monitor for additional guidance, as needed. Completion of bempegaldesleukin administration must occur within accepted timeframes (eg, from reconstitution or from time bempegaldesleukin is brought to room temperature) as described in the Pharmacy Manual.

6.5.1.1.2 Elevated Hepatic Transaminases: Monitoring and Management

Elevated hepatic transaminases are a toxicity that can occur for bempegaldesleukin. The elevations in hepatic transaminases associated with bempegaldesleukin typically occur at the time of peak of bempegaldesleukin active metabolite concentrations in the blood (Days 4-8), and are often accompanied by other cytokine-related toxicities such as flu-like symptoms, rash or pruritus. The transient elevations in hepatic transaminases are usually mild or moderate in severity, not associated with increased total bilirubin, resolve spontaneously without treatment, and predominantly occur in Cycle 1 and Cycle 2.

The following recommendations are for patients randomized to Arm A receiving bempegaldesleukin and apply to Cycle 1 only. Patients on subsequent cycles of bempegaldesleukin should follow the guidance in Table 6 (Section 6.5.2.1.2). These recommendations are not intended to serve as rigid guidelines or to replace clinical judgment, and do not apply to patients receiving pembrolizumab monotherapy. Hepatic events, including elevated liver function tests, have also been observed for pembrolizumab; for patients receiving pembrolizumab monotherapy, see Table 6 (Section 6.5.2.1.2).

For patients experiencing elevated hepatic transaminases while receiving Cycle 1 of bempegaldesleukin alone or in combination with pembrolizumab, first rule out non-inflammatory etiologies. If non-inflammatory cause, treat accordingly and continue bempegaldesleukin. Consider imaging if obstruction is suspected.

If during monitoring alanine transaminase (ALT)/aspartate transaminase (AST) increases, follow the guidance for the highest levels.

AST or ALT > 3.0 to ≤ 5.0 × upper limit of normal (ULN)

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

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

ALT or AST > 5.0 to ≤ 8.0 × ULN

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

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

If no improvement within 7 days:

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

ALT or AST > 8.0 × ULN

- Discontinue bempegaldesleukin and pembrolizumab
- Increase frequency of monitoring to approximately 1-2 days
- 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least one month
- Consult gastroenterologist
- If no improvement in > 3–5 days, worsens or rebounds, add non-corticosteroid immunosuppressive medication
- Additional guidance is provided in Table 6 (Section 6.5.2.1.2)

Additionally, any bempegaldesleukin-related liver function test abnormality that meets the following criteria requires discontinuation of bempegaldesleukin:

- Total bilirubin > 5 × ULN
- Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN

6.5.1.1.3 Immune-Related Adverse Events and Cytokine-Mediated Toxicity: Monitoring and Management

Management algorithms for immune-related AEs (irAEs, which are also referred to as immune-mediated AEs [imAEs] in this document) are provided in Section 6.5.2.1.2.

Cytokine-release syndrome (CRS) is a clinical diagnosis presenting usually with a constellation of symptoms often characterized by but not limited to, persistent fever, hypotension, dyspnea associated with or without tachypnea, headache, tachycardia, and rash caused by the release of cytokines. End organ dysfunction with varied manifestation can be seen in CRS as well. Many of these symptoms overlap with known AEs seen in bempegaldesleukin and checkpoint inhibitors combination therapy (ie, pyrexia and hypotension). These symptoms may be seen in infusion reactions as well as other known syndromes, such as tumor lysis syndrome and macrophage activation syndrome. Note:

- For suspected, serious AE of CRS of Grade ≥ 3, the Investigator is required to contact the Sponsor.
- For patients in Arm A receiving bempegaldesleukin: an algorithm for the management of CRS is provided Appendix 6.

6.5.1.1.4 Monitoring and Management of Bempegaldesleukin-Induced Eosinophilia for Patients in Arm A Receiving Bempegaldesleukin:

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

For patients in Arm A receiving bempegaldesleukin: absolute eosinophil count should be closely monitored per protocol. If a study patient is suspected to have eosinophilic disorder (symptoms may involve skin, lungs, digestive tract, heart, blood, or nervous systems) with absolute eosinophil count at or above 5000/μL (5×10^9/L) level, bempegaldesleukin treatment may need to be withheld, and the patient should be treated as clinically indicated (Table 4).

Table 4: Management of Bempegaldesleukin-Induced Eosinophilia For Patients in Arm A Receiving Bempegaldesleukin

Event		
Absolute Eosinophil Value	**Symptomatic?[a]**	**Clinical Management**
≥ 5000/μL (5×10^9/L)	Yes	Bempegaldesleukin may need to be withheld; treat patient symptoms as clinically indicated.

a. Symptoms may involve skin, lungs, digestive tract, heart, blood, and nervous systems.

6.5.1.2 Bempegaldesleukin Dose Delay and Reduction Criteria

Dose delays and one dose reduction are permitted for bempegaldesleukin. Bempegaldesleukin may be delayed or reduced to 0.003 mg/kg based on observed drug-related toxicities. Medical Monitor consultation is required for dose reduction. For patients who have a dose reduction to 0.003 mg/kg: if the toxicity requiring dose reduction has resolved, bempegaldesleukin 0.006 mg/kg may be reinstated after a careful risk assessment.

Bempegaldesleukin may be delayed or reduced for the following reasons:

- For infusion reactions, refer to Section 6.5.2.1.1.
- For irAEs, refer to Section 6.5.2.1.2.
- Grade ≥ 2 creatinine increase:
  - For patients who must delay study treatment due to Grade ≥ 2 creatinine increase due to a non-inflammatory cause, delay retreatment with study drug for approximately 3 to 5 days. After the dosing delay, the patient may resume study drug when serum creatinine has returned to Grade ≤ 1, as assessed within 24 hours prior to redosing (or as soon as locally feasible, except where permanent discontinuation of study drug is required [see Section 6.5.1.3]).
- Grade ≥ 3 toxicity at least possibly related to bempegaldesleukin: bempegaldesleukin must be delayed until resolution to Grade 1 or baseline (unless otherwise requiring permanent discontinuation per Section 6.5.1.3), patients with the following laboratory values can continue study drug:
  - Grade ≥ 3 lymphopenia
  - Grade ≥ 3 asymptomatic amylase or lipase elevation
- Patient has acute infection (eg, fever, upper or lower respiratory tract infection) requiring systemic antibiotic therapy. Patient may resume study treatment once free of signs or symptoms for 72 hours after completion of antibiotic therapy.
- For eosinophilia, refer to Section 6.5.1.1.4.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

Bempegaldesleukin dosing may resume at the same bempegaldesleukin dose or at the lower bempegaldesleukin dose level when toxicity resolves to Grade ≤ 1 or returns to baseline, except for instances where the potential recurrence of the event poses an undue risk for the patient.

6.5.1.3 Bempegaldesleukin Discontinuation Criteria

For toxicities requiring discontinuation of treatment with bempegaldesleukin, pembrolizumab alone may continue as a monotherapy if the toxicity is considered by the Investigator to be not related to pembrolizumab.

For CVA events and suspected TIA events, follow the criteria described below (additional details are provided in the CVA management algorithm in Appendix 2).

Bempegaldesleukin treatment should be permanently discontinued for the following:

- For infusion reactions, in accordance with the criteria in Section 6.5.2.1.1.
- For irAEs, in accordance with the criteria in Section 6.5.2.1.2.
- For any Grade 4 drug-related AE or clinically significant laboratory abnormality, with the exception of the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days.
  - Grade 4 lymphopenia or leukopenia ≤ 14 days in duration.
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to Grade < 4 or return to baseline within 7 days.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued treatment.
- Any new CVA event confirmed by imaging (diffusion-weighted imaging [DWI] MRI preferred unless otherwise contraindicated) regardless of neurological symptoms (eg, cryptogenic CVA) and for a suspected TIA event without clear alternative etiology (see Appendix 2).

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

6.5.2 Pembrolizumab

6.5.2.1 Dose Modification (Withhold, Treat, Discontinue) and Toxicity Management for Specific Adverse Events

6.5.2.1.1 Infusion Reactions

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reactions are provided in Table 5.

These guidelines apply to patients receiving **bempegaldesleukin in combination with pembrolizumab OR either pembrolizumab or bempegaldesleukin treatment as a**

monotherapy. For toxicities requiring treatment discontinuation, bempegaldesleukin or pembrolizumab alone may continue as a monotherapy if the toxicity is considered not related to that study drug by the Investigator.

Table 5: Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	**Pembrolizumab monotherapy**: None **Bempegaldesleukin alone or in combination with pembrolizumab**: Patient may be premedicated 1.5 hours (± 30 minutes) prior to infusion of study intervention with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Patient may be premedicated 1.5 hours (± 30 minutes) prior to infusion of study intervention with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. ** In cases of anaphylaxis, epinephrine should be used immediately. Patient is permanently discontinued from further study drug intervention.	No subsequent dosing

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = by mouth

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov

6.5.2.1.2 Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6. These guidelines apply to patients **receiving bempegaldesleukin in combination with pembrolizumab OR either treatment as a monotherapy**.

For toxicities requiring treatment discontinuation, bempegaldesleukin or pembrolizumab alone may continue as a monotherapy if the toxicity is considered not related to that study drug by the Investigator.

For patients in Arm A receiving bempegaldesleukin, elevations of AST or ALT occurring in Cycle 1 should be managed according to the guidelines in Section 6.5.1.1.2. For elevations of AST or ALT occurring in Cycle 2 or beyond, follow the dose modification and toxicity management guidelines in Table 6.

Table 6: Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Study Treatment

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study treatment must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study treatment has been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action with Study Treatment	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor patients for signs and symptoms of pneumonitis • Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action with Study Treatment	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor patients for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Patients with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Patients with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin[f]	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of b-cell failure	Withhold [d]	• Initiate insulin replacement therapy for patients with T1DM • Administer anti-hyperglycemic in patients with hyperglycemia	• Monitor patients for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action with Study Treatment	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3, 4	Permanently discontinue		
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Abbreviations: AE(s) = adverse event(s); ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DRESS = drug reaction with eosinophilia and systemic symptoms; GI = gastrointestinal; irAE = immune-related adverse event(s); IV = intravenous; SJS = Stevens-Johnson Syndrome; T1DM = type 1 diabetes mellitus; TEN = toxic epidermal necrolysis; ULN = upper limit of normal

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

a. AST/ALT: > 3.0 - 5.0 × ULN if baseline normal; > 3.0 - 5.0 × baseline, if baseline abnormal;
bilirubin:> 1.5 - 3.0 × ULN if baseline normal; > 1.5 - 3.0 × baseline if baseline abnormal

b. AST/ALT: > 5.0 to 20.0 × ULN, if baseline normal; > 5.0 - 20.0 × baseline, if baseline abnormal;
bilirubin:> 3.0 - 10.0 × ULN if baseline normal; > 3.0 - 10.0 x baseline if baseline abnormal

c. AST/ALT: > 20.0 × ULN, if baseline normal; > 20.0 × baseline, if baseline abnormal;
bilirubin: >10.0 × ULN if baseline normal; > 10.0 × baseline if baseline abnormal

d. The decision to withhold or permanently discontinue study treatment is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, study treatment may be resumed.

e. Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis, sclerosing cholangitis).

f. For patients in Arm A receiving bempegaldesleukin in Cycle 1, consult the guidelines in Section 6.5.1.1.2.

6.5.2.1.3 Elevated Transaminases With Treated HBV or HCV

Patients who were treated for HBV or HCV, enrolled in the study, and present with elevated transaminases according to the criteria below should be evaluated for viral hepatitis exacerbation/reactivation.

- If baseline AST/ALT < 2 × ULN and increase of AST/ALT ≥ 5 × ULN
- If baseline AST/ALT ≥ 2 × ULN and increase of AST/ALT > 3 × baseline level
- AST/ALT > 500 U/L regardless of baseline

Viral load testing and additional hepatitis serologies should be included as required.

6.5.3 Other Allowed Dose Interruptions

Bempegaldesleukin and/or pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Medical Monitor. The reason for study intervention interruption is to be documented in the patient's study record.

6.6 Discontinuation Criteria

Study treatment must be permanently discontinued but patients will continue to be monitored in the study for any of the following reasons:

- Patient’s request to stop study treatment. Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for further assessments or contact with him/her or persons previously authorized by patient to provide this information.
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the patient.
- Any study treatment-related toxicity specified as a reason for permanent discontinuation as defined in the study treatment discontinuation criteria specific to bempegaldesleukin in Section 6.5.1.3 and in the guidelines for dose modification due to AEs in Section 6.5.2.1.
- Termination of the study by the Sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, a patient who has been imprisoned may be permitted to continue as a patient. Strict conditions apply and Sponsor approval is required.)

- Disease progression in the absence of clinical benefit as determined by the Investigator (see Section 6.2.5 for information regarding treatment beyond progression).
- Occurrence of a clinically significant AE found to be unacceptable or nonresolution of a clinically significant AE for > 8 weeks.
- Symptomatic deterioration in the absence of tumor progression per RECIST 1.1.
- Noncompliance of the patient with protocol-mandated procedures based on the judgment and agreement of both the Investigator and Sponsor.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.5, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the patient will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The patient has a medical condition or personal circumstance which, in the opinion of the Investigator and/or Sponsor, places the patient at unnecessary risk from continued administration of study intervention.
- Patient is lost to follow-up (as defined in Section 6.2.7).

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

Patients may choose to discontinue the study at any time, for any reason, and without prejudice to further treatment.

In the event of a patient's withdrawal, the Investigator will make every effort to complete the post-treatment assessments specified in the Schedule of Events (Section 1.2). If a patient has not progressed following discontinuation of study drug(s), every effort should be made to continue to obtain radiographic tumor assessments (until the patient has documented progression as per the BICR).

If a female patient becomes pregnant, administration of the study drug(s) must be discontinued immediately and the Investigator must notify the Sponsor within 24 hours of awareness of the pregnancy. Refer to Section 10.16 (Pregnancy).

All patients who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 1.2. The only exception to this requirement is when a patient withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

6.7 Prior and Concomitant Medications/Procedures

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study drug and up to 30 days after the last dose of study drug (Follow-Up Visit 1) will be documented and recorded. In addition:

- Prior cancer treatments, including previous immunotherapy, chemotherapy, targeted therapy, radiation, over-the-counter (OTC) medications, herbs, and dietary supplements will be recorded.
- Any COVID-19 vaccinations administered to patients prior to signing the ICF and during the treatment phase should be captured in the eCRF per the eCRF completion guidelines.
- All concomitant medications administered during SAEs (defined in Section 10.6), AESIs (defined in Section 10.12), or Events of Clinical Interest (ECIs; defined in Section 10.14) are to be recorded.

6.7.1 Premedication

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

If a patient experiences a Grade 1 or 2 infusion reaction during any infusions with bempegaldesleukin or pembrolizumab, prophylactic premedications may be administered for subsequent infusions (see Section 6.5.2.1.1 for further details on management and prevention of infusion reactions).

Please refer to Section 6.7.3.2 for additional recommendations regarding infusion reaction prophylaxis.

For patients in Arm A receiving bempegaldesleukin: refer to Section 6.2.3.2 for hydration guidance.

6.7.1.1 Premedications for Flu-Like Symptoms Associated with Bempegaldesleukin

For patients in Arm A receiving bempegaldesleukin, prophylaxis for flu-like symptoms with either acetaminophen or NSAIDs is permitted on study per the Investigator's discretion. Prophylaxis for flu-like symptoms should be initiated on either Day 1 or Day 2 of the dosing cycle and may continue through Day 5 or longer as needed. These premedications do not apply to patients receiving pembrolizumab monotherapy.

6.7.2 Prohibited and/or Restricted Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The Investigator is to discuss prohibited medication/vaccination with the Medical Monitor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study intervention requires the mutual agreement of the Investigator, the Sponsor, and the patient.

6.7.2.1 Prohibited Medications

Patients are prohibited from receiving the following therapies during the screening and treatment periods of this study:

- Immunosuppressive agents or immunotherapy not specified in this protocol.
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.7.3.1) defined as a daily dose of > 10 mg prednisone equivalents.
- Radiation for disease control.
  Note: Palliative radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator's discretion.
- Antineoplastic systemic chemotherapy or biological therapy is prohibited during the study.
- Investigational agents other than pembrolizumab or bempegaldesleukin.
- Live or attenuated vaccines 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; coronavirus virus disease 2019 [COVID-19]).
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

In addition, prohibited medications listed in the current pembrolizumab prescribing information are not allowed. If the Investigator determines that a patient requires any of the aforementioned treatments for any reason, all study intervention must be discontinued.

6.7.2.2 Blood Pressure Medications for Patients Receiving Bempegaldesleukin

For patients in Arm A receiving bempegaldesleukin:

- Consideration should be given to withholding antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (eg, alpha blockers for benign prostatic hyperplasia), particularly when therapy involves multiple antihypertensive drugs and classes other than thiazide diuretics. If withholding antihypertensive medications, withhold no less than 12 hours and no more than 48 hours prior to each dose of bempegaldesleukin.
- Patients who are receiving medications with antihypertensive effects for the treatment of coronary artery disease (eg, β-blockers, calcium channel blockers, nitrates, etc.) should be able to withhold these drugs prior to initiation of treatment at the Investigator's discretion.
- Antihypertensive medications may be reinstituted in between doses of bempegaldesleukin at any time as clinically indicated (eg, based on blood pressure monitoring results).
- For patients receiving β-blockers, consider a step-wise tapering of doses before initiation of bempegaldesleukin to avoid reflex tachycardia. If Grade ≥ 2 hypertension is observed in any cycle, patients should be monitored more frequently (at least weekly) until a new stable antihypertensive regimen is identified. Patients may be monitored more frequently at the discretion of the Investigator as clinically warranted.

6.7.3 Permitted Concomitant Medications

6.7.3.1 Steroids

Systemic glucocorticoids are permitted only for the following purposes:

- To modulate symptoms of an AE that is suspected to have an immunologic etiology
- As needed for the prevention of emesis
- Premedication for IV contrast allergies
- Short-term oral or IV use in doses > 10 mg/day prednisone equivalent for chronic obstructive pulmonary disease (COPD) exacerbations
- For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

In addition, the following glucocorticoid use is allowed:

- For topical use or ocular use
- Intraarticular joint use
- For inhalation in the management of asthma or chronic obstructive pulmonary disease

Patients with pre-existing adrenal impairment requiring corticosteroid supplementation may be at increased risk for hypotensive episodes during treatment with bempegaldesleukin and may

require co-management with an endocrinologist. For these patients, their existing corticosteroid dose may be increased to adrenal replacement steroid doses > 10 mg of daily prednisone or equivalents for the first 4 days after administration of bempegaldesleukin based on an assessment of the degree of adrenal impairment and the extent of existing corticosteroid supplementation.

A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, pneumonia, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Use of corticosteroids for the management of immune-related AEs as outlined in Section 6.5.2.1.2 is permitted. Short-term use of systemic corticosteroids or immunosuppressive medication is permitted if administered for AE treatment.

6.7.3.2 Prophylaxis

Prophylaxis for flu-like symptoms and rash and/or pruritus can be initiated on either Day 1 or 2 of the dosing cycle and may continue through Day 5 or longer as needed at the discretion of the Investigator as follows for:

- Flu-like symptoms: prophylactic use of either acetaminophen (paracetamol) or non-steroidal anti-inflammatory agents (eg, ibuprofen) is permitted.
- Rash and/or pruritus: prophylactic use of antihistamines is permitted.

As appropriate, additional treatment measures may be provided based on local treatment standards and guidelines (see Section 6.5.2.1.1).

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

6.7.3.3 Thromboembolism Prophylaxis and Treatment for Patients Receiving Bempegaldesleukin

Patients in Arm A receiving bempegaldesleukin with a history of a venous or arterial thromboembolic event must be receiving a stable regimen of therapeutic anticoagulation (preferably LMWH or DOAC). Unless there is a new medical contraindication observed after Cycle 1 Day 1, a patient with a history of venous or arterial thromboembolic event must be maintained on therapeutic anticoagulation throughout the patient's time on study treatment (ie, through discontinuation of all study drug[s]).

- Use of warfarin is permitted; however, therapeutic dosing should target a specific international normalized ratio (INR) stable for at least 4 weeks prior to enrollment. Because bempegaldesleukin has the potential to downregulate metabolizing enzymes for warfarin for approximately 1 week after administration of each dose of bempegaldesleukin, frequent monitoring of INR especially during the first 7 days after bempegaldesleukin administration and ongoing consideration of warfarin dose adjustments are warranted for all patients receiving bempegaldesleukin throughout the patient's participation in the study.

6.7.3.4 Rescue Medications, Palliative and Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of infusion-related AEs and AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.5.2.1.1 and Section 6.5.2.1.2.

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

6.7.4 Effect of Bempegaldesleukin on the PK of Concomitant Medications

Clinical drug interaction studies with bempegaldesleukin have not been performed. Bempegaldesleukin may have the potential to affect the clearance of co-administered drugs based on its ability to modulate cytokines. Bempegaldesleukin causes increases in circulating cytokines typical of those associated with an acute inflammatory response to infection or tissue injury. The increases in inflammatory cytokines induced by bempegaldesleukin are generally moderate, persist for about one week after bempegaldesleukin dosing, and return to baseline levels prior to the next dose. Several of these cytokines (IFN-γ, IL-6, IL-10, etc.) have the potential to decrease the activity of multiple enzymes and drug transporters, and the suppressive effects can be additive (Haas 2005; Zidek 2009). Similar to changes that occur during a typical inflammatory response, bempegaldesleukin may lead to downregulation of drug metabolizing enzymes, such as cytochrome P450 (CYP) enzymes, hepatic flavin monooxygenases, uridine 5'-diphospho–glucuronosyltransferases (UDP-glucuronosyltransferases), sulfotransferases, and glutathione S-transferases. Consequently, treatment with bempegaldesleukin may lead to temporary decrease in clearance of drugs that are substrates of drug metabolizing enzymes, or drug transporters. Investigators should carefully monitor for occurrence of adverse effects in patients receiving drugs with narrow therapeutic indices or drugs that are sensitive substrates of drug metabolizing enzymes or drug transporters, and adjust the dose of these drugs as clinically indicated.

6.7.4.1 Interaction of Bempegaldesleukin and Warfarin

Bempegaldesleukin has the potential to down-regulate metabolizing enzymes for warfarin for approximately 1 week after administration of each dose of bempegaldesleukin. See Section 6.7.3.3 for guidelines on monitoring of INR in patients using warfarin.

6.8 Adverse Events

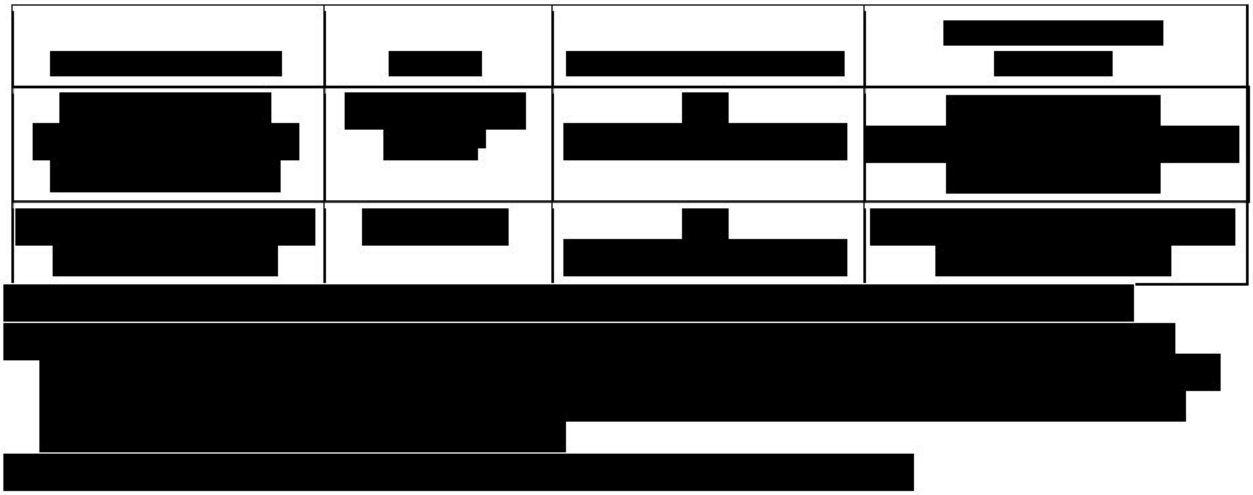
For reporting of AEs, see Section 10.5.

For reporting of SAEs, see Section 10.7.

7.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

Table 7 provides the study treatments that will be administered in the study.

Table 7: Study Treatments Administered



7.1 Bempegaldesleukin (NKTR-214)

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

7.1.1 Drug Description and Formulation

7.1.2 Drug Packaging and Labeling

ials may be packaged as a single vial or multiple vials per carton and labeled according to current good manufacturing practices.

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

7.1.3 Drug Reconstitution and Handling

Bempegaldesleukin [redacted]

The instructions for reconstitution, preparation, and administration of bempegaldesleukin (NKTR-214) drug product are described in the Pharmacy Manual.

7.1.4 Drug Storage

[redacted]

7.1.5 Drug Shipment

For all countries, the Sponsor will supply bempegaldesleukin from a central source. Refer to the Pharmacy Manual for additional details for ordering drug supply.

7.2 Pembrolizumab Preparation, Storage, and Packaging

Refer to the Pharmacy Manual for details.

7.3 Study Drug Accountability and Reconciliation

Bempegaldesleukin and pembrolizumab are considered Investigational Medical Products and will be supplied to the Investigator by Nektar Therapeutics or its designee. Depending on local health authority guidelines and drug availability, pembrolizumab may be obtained through commercial supply, the site pharmacy, or through a central depository. Depending on source of supply per specific country requirements, the packaging and labeling may vary. Products will be labeled to meet local country requirements. Please refer to the Pharmacy Manual for detailed information.

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

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

The Drug Accountability Log may record specifics to study drug (ie, bempegaldesleukin or pembrolizumab) dispensation such as:

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

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

8.0 STUDY ASSESSMENTS AND PROCEDURES

8.1 Tumor Imaging and Assessment of Disease

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

Tumor response will be evaluated using RECIST 1.1 described in Section 9.1.

The process for image collection and transmission to the central vendor can be found in the Site Imaging Manual. Tumor imaging may be performed by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI), but the same imaging technique should be used in a patient throughout the trial. CT scan is the more commonly used modality and is preferred for the majority of patients. An MRI can be utilized if clinically appropriate.

Imaging should include the head, neck, chest, and abdomen at all time points specified in Section 1.2. Imaging of the pelvis is optional unless clinically indicated. A CT from the vertex of the head to the thoracic inlet or a brain CT is strongly preferred. For an individual patient, imaging should be consistent at all time points (ie, follow-up scans should image the same areas as the baseline area, using the same imaging modality).

Local reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine patient eligibility. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, a maximum of 10 target lesions in total and 5 per organ are allowed. All scheduled images for all study patients from the sites will be submitted to the central imaging vendor. In addition, additional imaging (including other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, should be submitted to the central imaging vendor as well.

The central imaging vendor will receive radiologic images for a retrospective analysis of patient baseline disease and treatment response. In addition, radiologic progression will be based on the independent central assessment of progression, rather than site assessment. The central imaging vendor will verify progressive disease (PD) following first radiologic evidence of PD assessed by the local site investigator. Verification of radiologic progression applies to both treatment arms. Expedited verification of radiologic progression as determined by central review (following site assessment of progression) will be communicated to the site (see Section 8.1.3).

8.1.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days prior to the date of randomization. The site study team must review pre-trial images to confirm the patient has measurable disease per RECIST 1.1.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of randomization.

8.1.2 Tumor Imaging During the Study

Imaging should be performed every 6 weeks (42 days ± 7 days) from the date of randomization or more frequently if clinically indicated. One year after randomization, patients who remain on treatment will have imaging performed every 9 weeks (± 14 days). This imaging schedule should be maintained regardless of treatment delays or other changes in treatment schedule.

The scan for confirmation of partial response or complete response may be performed at the earliest 4 weeks after the date the response was first documented, or at the next scheduled scan (ie, 6 weeks later), whichever is clinically indicated. Imaging should then return to the original schedule beginning with the next protocol-specified time point.

Patients who obtain a confirmation scan at 4 weeks do not need to undergo the next scheduled imaging assessment if it is due < 4 weeks later; imaging may resume at the subsequent scheduled time point.

Continue to perform imaging until whichever of the following occurs first:

- Initial site-assessed disease progression is verified by the central imaging vendor.
- The start of new anticancer treatment
- Withdrawal of consent
- Death
- The end of the study

Note: If the site-assessed disease progression is verified by the central imaging vendor, it is the discretion of the Investigator to continue to treat the patient (see Section 6.2.5) and follow the regular imaging schedule intervals until progression is confirmed provided the patient meets the conditions detailed in Section 8.1.3.

8.1.3 Assessment of Disease

RECIST 1.1 will be applied by the central imaging vendor as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study therapy). Scans showing site-assessed progressive disease should be submitted to the central imaging vendor immediately. The site will be notified if the imaging vendor verifies disease progression using RECIST 1.1.

Section 6.3.1 provides additional information about the Follow-up Visits.

8.2 Pharmacokinetic and Immunogenicity Measurements

Pharmacokinetic (PK) and immunogenicity (IMG) assessment data will be collected from study patients randomized to Arm A (bempegaldesleukin plus pembrolizumab) depending on the Phase of the study as follows:

- See Table 8 for patients randomized in the Phase 2 portion of the study.
- See Table 9 for patients randomized in the Phase 3 portion of the study.

All time points are relative to the start of each study drug administration, unless indicated otherwise. All on-treatment time points are intended to align with days on which study drug is administered; if dosing occurs on a different day, the PK and IMG 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. All predose samples should be collected within 24 hours before the start of any dose infusion.

Further details of sample collection, processing, and shipment will be provided in the Laboratory Manual.

Serum PK samples will be analyzed for pembrolizumab by a validated ligand binding assay. Plasma PK samples will be analyzed for NKTR-214 related molecules with a validated or qualified ligand-binding assay.

Validated methods will be used to detect anti-drug antibodies (ADA) as determined by measurements of anti-pembrolizumab, anti-bempegaldesleukin, and anti-IL-2 in the immunogenicity samples. Immunogenicity sample testing will be done in tiers as per the 2019 FDA guidance (FDA 2019). Samples will be first tested with screening electrochemiluminescence assays (ECLA). Putative positive samples for anti-pembrolizumab, anti-bempegaldesleukin, or anti-IL-2 ADA will then be analyzed in a competition ECLA to confirm positivity. Confirmed anti-bempegaldesleukin ADA positive samples will be tested further in a PEG immuno-competition assay to determine the antibody specificity of the reactivity to the PEG or non-PEG (IL-2, linker) moiety of bempegaldesleukin. Confirmed positive samples from anti-pembrolizumab, anti-bempegaldesleukin and anti-IL-2 ADA assays will then be tested to obtain a titer. Samples confirmed to be positive for anti-pembrolizumab, anti-bempegaldesleukin and anti-IL-2 ADA may also be tested for neutralizing activity for IL-2 and pembrolizumab using validated cell-based assays.

Blood samples designated for assessments (eg, immunogenicity, PK) from the same collection time point may be used interchangeably for analyses, if required (eg, insufficient volume for complete assessment, to follow-up on suspected immunogenicity related AE, etc.). Blood samples or plasma isolated from blood samples for assessments (eg, immunogenicity, PK) may be assessed by ELISA, seromics, microRNA profiling, metabolomics and/or other relevant multiplex-based protein assay methods for immune-related factors that may predict for pembrolizumab and/or bempegaldesleukin benefit or AEs; [redacted]

[redacted]

Additionally, residual blood samples will be archived and may be used for potential exploratory analysis (eg, analysis of ADA immune complexes, exploratory PK) and/or for additional method purposes (eg, cross-validation, ADA/PK selectivity, cut point etc.).

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

Table 8: Phase 2 Portion of the Study: Pharmacokinetic and Immunogenicity Sampling (for Arm A [Bempegaldesleukin plus Pembrolizumab])

Study Day of Sample Collection (1 Cycle = every 3 weeks)	Event	Time (relative to start of bempegaldesleukin infusion) Hour:Min	Bempegaldesleukin Blood Sample		Pembrolizumab Blood Sample	
			PK[d]	IMG	PK	IMG
Cycle 1 Day 1	Predose[a]	00:00	X	X	X	X
	EOI[b]	00:30[b]	X			
Cycle 1 Day 3[c]		48:00[c]	X			
Day 1 of Cycles 2, 5, 8, 11, 17, 25, and 33	Predose[a]	00:00	X	X	X	X
Follow Up Visit 1, 30 (± 7) days from last dose of all study drugs			X	X	X	X
Follow Up Visit 2, 90 (± 7) days from last dose of all study drugs			X	X	X	X

Abbreviations: EOI = end of infusion; IMG = immunogenicity; PK = pharmacokinetic

a. Predose samples should be collected within 24 hours before the start of any dose infusion.
b. The end of infusion sample should be taken up to 30 minutes after the end of the bempegaldesleukin infusion. End of infusion samples may not be collected from the same IV access as drug was administered. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.
c. Time window for Day 3 is −1 day (ie, 24 to 48 hours from the start of bempegaldesleukin infusion).
d. The bempegaldesleukin PK blood samples may also be used for assessing inflammatory cytokines and chemokines (see Section 8.2 for more details).

Table 9: Phase 3 Portion of the Study: Pharmacokinetic and Immunogenicity Sampling (for Arm A [Bempegaldesleukin plus Pembrolizumab])

Study Day of Sample Collection (1 Cycle = every 3 weeks)	Event	Time (relative to start of bempegaldesleukin infusion) Hour:Min	Bempegaldesleukin Blood Sample		Pembrolizumab Blood Sample	
			PK[e]	IMG	PK	IMG
Cycle 1 Day 1	Predose[a]	00:00	X	X	X	X
	EOI[b]	00:30[b]	X			
Cycle 1 Day 3[c]		48:00[c]	X			
Cycle 1 Day 5[d]		96:00[d]	X			
Day 1 of Cycles 2, 5, 8, 11, 17, 25, and 33	Predose[a]	00:00	X	X	X	X
Follow Up Visit 1, 30 (± 7) days from last dose of all study drugs			X	X	X	X
Follow Up Visit 2, 90 (± 7) days from last dose of all study drugs			X	X	X	X

Abbreviations: EOI = end of infusion; IMG = immunogenicity; PK = pharmacokinetic

a. Predose samples should be collected within 24 hours before the start of any dose infusion.
b. The end of infusion sample should be taken up to 30 minutes after the end of the bempegaldesleukin infusion. End of infusion samples may not be collected from the same IV access as drug was administered. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.
c. Time window for Day 3 is −1 day (ie, 24 to 48 hours from the start of bempegaldesleukin infusion).
d. Time window for Day 5 samples is ± 1 day (ie, 72 to 120 hours from the start of bempegaldesleukin infusion).
e. The bempegaldesleukin PK blood samples may also be used for assessing inflammatory cytokines and chemokines (see Section 8.2 for more details).

[redacted]

Table 10: Tumor Tissue [redacted]

Study Day of Sample Collection (1 Cycle = every 3 weeks)	Event	Tumor Tissue Collection	[redacted]
Screening		X[a]	
Cycle 1 Day 1	Predose[b]		[redacted]
Cycle 3 Day 1	Predose[b]		[redacted]
Cycle 5 Day 1	Predose[b]		[redacted]
Follow Up Visit 1, 30 (± 7) days from last dose of study drug			[redacted]

[redacted]

a. See Section 8.3.1.
b. Predose samples should be collected within 24 hours before the start of any dose infusion.

8.3.1 Tumor Tissue Collection and Assessments

All patients must have tumor tissue available to be sent to the central laboratory during the Screening period:

- A newly obtained core, incisional, or excisional biopsy of a tumor lesion that was not previously irradiated (recurrent lesions in a previously irradiated area can be biopsied if progression has been shown in such lesions since irradiation).

  OR

- An archival tumor tissue sample from a recurrent lesion with no intervening treatment or radiation (recurrent lesions in a previously irradiated area can be biopsied if progression has been shown in such lesions since irradiation) between time of acquisition and randomization.

Newly obtained biopsies are preferred to archived tissue.

Archival tumor tissue should be provided in a formalin-fixed paraffin-embedded (FFPE) block (obtained within 12 months of randomization) or as unstained slides (minimum of 8 slides, preferably 15-25 slides) obtained within 4 months (if stored in the dark at room temperature up to 25°C) or 6 months (if stored in the dark at 2°C–8°C) of randomization. If 8 unstained slides are not available, fewer slides may be submitted; please contact the Medical Monitor for written approval. Leftover tissue blocks, but not slides, will be returned upon request.

Biopsy in bone lesions cannot be accepted. Fine needle aspirates/biopsy or other cytology specimens are insufficient. Target lesions should not be biopsied unless there are no other lesions suitable for biopsy.

PD-L1 status will be determined by a local laboratory or the central laboratory. The tissue sample will be used to ascertain PD-L1 status using the PD-L1 IHC 22C3 PharmDx diagnostic

kit. The PD-L1 IHC 22C3 PharmDx assay kit is currently approved to assess PD-L1 status in patients with HNSCC for treatment with pembrolizumab. The 22C3 PharmDx evaluations will determine CPS, which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen will be considered to have positive PD-L1 expression if CPS ≥ 1. Repeat samples may be required if adequate tissue is not provided for assessment of PD-L1 status; additional details of sample collection, processing, and shipment will be provided in the Laboratory Manual.

The PD-L1 result will not be masked to the site.

[redacted]

8.3.1.1 Patients with Oropharyngeal Cancer: Collection of Tumor Tissue for HPV Status

Patients with oropharynx cancer must have assessment of HPV status from tumor tissue prior to randomization. HPV stratification in this trial may be performed using local testing of HPV status in patients with oropharynx cancer using the specified method.

> Note: Tumor p16 expression must be evaluated by assessment of IHC analysis with CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ) using 'Benchmark Ultra' autostainer (Ventana, Tucson, AZ) and standard protocol. Positive p16 expression is defined as strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells.
>
> Note: If local p16 testing results are not available, or cannot be assessed by the specified method, a tumor tissue sample may be submitted for p16 testing at the designated central laboratory.

8.3.2 [redacted]

[redacted]

[redacted]

8.3.3 Additional Research and Sample Storage

This protocol will include residual sample storage for additional research. Residual samples from all PK, immunogenicity, [redacted] collections from all time points will be retained.

[redacted] Samples may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. [redacted]

- [redacted]
- [redacted]

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

Samples kept for future research will be stored at the Sponsor's Biorepository or an independent, Sponsor-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 15 years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research Sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

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

8.4 Health-Related Quality of Life (HRQoL)

The evaluation of patient-reported outcomes in oncology clinical trials is becoming increasingly important to understand the benefits and risks of treatment from a patient perspective. Patients will be asked to complete the EORTC QLQ-C30, EORTC QLQ-H&N35, and EuroQol EQ-5D as outlined in Section 1.2 to assess changes from baseline in patient-reported outcomes, which will be affected by both disease progression and treatment tolerability.

Refer to Section 9.2 for additional information.

9.0 ASSESSMENT OF EFFICACY

9.1 Assessment of Tumor Response and Progression

Response and progression will be determined by blinded independent central review (BICR) using RECIST 1.1 (Appendix 4). Screening and follow-up images should be acquired as outlined in Section 1.2 (Schedule of Events).

9.2 Patient-Reported Outcomes

Section 1.2 provides the schedule for the health-related quality of life (HRQoL) assessments, EORTC QLQ-C30, EORTC QLQ-H&N35, and EuroQol EQ-5D.

If the patient withdraws from the study prematurely, all attempts should be made to obtain a final quality of life questionnaire prior to patient discontinuation. Reasons for missing patient-reported outcome questionnaires should also be documented so that the appropriate imputation method can be employed to correct for missing data in the analysis.

The questionnaires will be completed by the patients before any clinical assessments are performed and treatments administered at any given visit. It is a best practice and strongly recommended that patient-reported outcome (PRO) questionnaires are administered to patients prior to drug administration, AE event evaluation, and disease status notification. If patients refuse to complete all or any part of a questionnaire, this will be documented. Questionnaires should be completed in the language most familiar to each patient, and patients should be given adequate time and space to complete the questionnaire.

The EQ-5D should be completed by patients first before completing the EORTC QLQ-C30 and EORTC QLQ-H&N35.

9.2.1 EQ-5D

The EuroQol-5D (EQ-5D) is a standardized instrument for use as a measure of health outcome. The EQ-5D will provide data for use in economic models and analyses including developing health utilities or quality adjusted life-years (QALYs).

The 5-level version of the EQ-5D (EQ-5D-5L) (EuroQol Group 1990; Herdman 2011) will be used to assess treatment effects on perceived health status and to generate utility data for health economic evaluations. The EQ-5D-5L is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 5 response levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

Responses to these 5 dimensions are converted into 1 of 3,125 unique EQ-5D health state descriptions, which range between no problems on all 5 dimensions (11111) to extreme problems on all 5 dimensions (55555). Using appropriate country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility index representing the

societal desirability of his or her own health. In addition, the EQ-5D includes a visual analogue scale (VAS) allowing a respondent to rate his/her health on a scale ranging from 0-100 with 0 being the worst health state imaginable and 100 being the best health state imaginable.

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

9.2.2 EORTC QLQ-C30 and EORTC QLQ-H&N35

The EORTC QLQ-C30 (Aaronson 1993) is the most commonly used quality of life instrument in oncology trials. The EORTC QLQ-C30 is composed of multi-item scales and single item measures. These include 5 functional scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, nausea/vomiting, and pain), a global health status/HRQoL scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale.

The EORTC QLQ-H&N35 is in use worldwide as one of the standard instruments for measuring quality of life in head and neck cancer patients (Mehanna 2006; Tschiesner 2008) and consists of 7 multi-item scales measuring pain in the mouth, problems with swallowing, senses, speech, social eating, social contact, and sexuality, and 11 single-item scales assessing problems with teeth, mouth opening, dry mouth, sticky saliva, coughing, feeling ill, use of analgesics, use of nutritional supplements, use of feeding tube, weight gain, and weight loss (Bjordal 1999; Bjordal 1994). The EORTC QLQ-C30 and EORTC QLQ-H&N35 are psychometrically and clinically validated instruments appropriate for assessing quality of life in patients with head and neck cancer. These instruments were used in the EXTREME registration trial (NCT00122460) comparing platin-5-fluorouracil alone versus combined with cetuximab as first-line treatment in recurrent or metastatic HNSCC, which led to the FDA approval of cetuximab monotherapy in patients with recurrent or metastatic HNSCC refractory to cisplatin (Bjordal 2000; Chera 2014). They were also used in the Phase 3 trial of patients with locoregionally advanced head and neck cancer receiving radiotherapy alone or radiotherapy plus cetuximab (Tschiesner 2008).

For the global health status/quality of life and function scales, a higher value indicates a better level of function; for symptom scales and items, a higher value indicates increased severity of symptoms. Prior literature indicates that head and neck pain and the ability to swallow are clinically relevant symptom measures in the recurrent or metastatic HNSCC population (Bjordal 2000; Chera 2014; Mesia 2010; Machiels 2014). Thus, time to deterioration in the pain and swallowing multi-item scales of the EORTC QLQ-H&N35, in addition to time to deterioration and mean change from baseline in global health status/quality of life scale of the EORTC QLQ-C30, will be evaluated as secondary objectives.

Both the EORTC QLQ-C30 and EORTC QLQ-H&N35 use a recall period of the past week.

10.0 ASSESSMENT OF SAFETY

10.1 AE Definition and Assessment

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

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

Adverse events, SAEs, and other reportable safety events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative). The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. 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.

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about AE occurrence.

For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

An AE does not include:

- A medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion); an AE is the underlying condition that leads to the procedure.
- Pre-existing diseases or conditions present or detected before start of study drug(s) administration that do not worsen or increase in severity or frequency after the administration of study drug(s).
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery for a condition that has not worsened on study, social and/or convenience admissions to grant families a respite in caring for a patient).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgical procedure(s) planned prior to informed consent to treat a pre-existing condition that has not worsened.

10.2 Monitoring AEs

All AEs will be assessed by the Investigator and recorded, including but not limited to, the following: the event term, the date of onset and resolution, seriousness, severity, relationship to study drug(s), outcome, treatment of the event, and action taken with the study drug(s). AEs will be reported starting immediately after the patient has been administered the first dose of study drug(s) until 30 days after the last dose of study drug(s). For serious AEs (SAEs), additional reporting requirements also apply (see Section 10.7).

An event occurring after the patient has provided informed consent, but before the first dose of study treatment or confirmed screen failure, will be collected as medical history unless the event is either new and attributed to protocol-mandated procedures by the Investigator or there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Under the latter 2 circumstances, the event will be considered an AE and will be captured as such.

- Example 1: Thrombophlebitis associated with a blood draw for assessments required prior to dosing per protocol is an event that is related to protocol-mandated procedures. In this scenario, the event of "thrombophlebitis" will be captured as an AE, and it will be documented as being "unrelated" to study drug(s), as applicable.
- Example 2: An ankle sprain following an unexpected fall from a flight of stairs while at home, after the patient has provided informed consent, but before the first dose of study drug(s), is clearly unrelated to any protocol-mandated procedures and would therefore be captured as medical history.

10.3 Grading of AEs

The severity of an event and the seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of event is based on the patient/event outcome or action criteria. All AEs will be assessed for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 guidelines. If a particular AE is not listed in the NCI-CTCAE, the following criteria will be used:

- Grade 1 = Mild (event results in mild or transient discomfort, not requiring or needing only minimal intervention or treatment; does not limit or interfere with daily activities [eg, insomnia, mild headache]).

- Grade 2 = Moderate (event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment [eg, fever requiring antipyretic medication]).
- Grade 3 = Severe (event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention).
- Grade 4 = Life threatening or disabling.
- Grade 5 = Death.

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

10.4 Causality Relationship of AEs

In combination therapy, it is often not possible to distinguish causal association of treatment-emergent AEs with specific study drug especially when both drugs contribute to activation of the body's immune mechanism. However, medical judgment is to be used to assess AEs based on unique immune activation pathways of each drug, time to onset from therapy drug administration, and known safety profiles of checkpoint inhibitors and IL-2 therapy. A general guidance on causal association assessment is provided below. In absence of clear evidence on causal association, relatedness is suggested to be assigned to both drugs after ruling out alternative etiologies based on medical history, concurrent illness, concomitant medications, etc. The relationship of each AE to each study drug (bempegaldesleukin or pembrolizumab) as applicable will be evaluated by the Investigator using the following definitions:

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

10.5 AE Reporting and Follow-up

After initiation of study drug treatment, all AEs (both nonserious and serious AEs) will be reported from the time of first study drug(s) administration until 30 days after the last dose of all study drug(s) (ie, (Follow-Up Visit 1) and only SAEs until 90 days after the last dose of all study drugs (ie, Follow-Up Visit 2). Additionally, AEs related to protocol-mandated procedures occurring between the signing of consent and first dose of study drug will be reported (see Section 10.2). Progression of the head and neck cancer under study and death related to the progression of this cancer will not be reported (see Section 10.9).

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames indicated in Table 11.

All ongoing AEs will be followed until resolution, the patient is lost to follow-up (as defined in Section 6.2.7), patient death, or until the Follow-Up Visit 2. If the AE has not completely resolved by the last Follow-Up Visit, the final outcome of these ongoing AEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

For specific instructions on identifying and reporting SAEs, see Sections 10.6 and 10.7.

Table 11: Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period[a]	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
NSAE	Report if: - due to protocol-specified intervention - causes exclusion	Report all	Not required	Per data entry guidelines
SAE including Cancer[b] and Overdose	Report if: - due to protocol-specified intervention - causes exclusion	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - patient has been exposed to any protocol-specified intervention (eg, procedure, washout) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
AESI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 24 hours of learning of event

Abbreviations: AESI = adverse event of special interest; DILI = drug-induced liver injury; ECI = Event of Clinical Interest; NSAE = nonserious adverse event; SAE = serious adverse event.

a. Follow-up period includes:
Follow-Up Visit 1: reported until 30 days after the last dose of all study drug(s) and
Follow-Up Visit 2: reported only for SAEs until 90 days after the last dose of all study drug(s).

b. A new cancer that is not a condition of the study indication.

10.6 Serious AE Definition

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

- Results in death.
  Note: Death is an outcome of an AE and not an AE in itself. All events leading to death, regardless of relationship to study drugs, that occur during the protocol-specified reporting period, must be reported with the exception of deaths attributed to disease progression (refer to Section 10.9).
- Is life threatening, that is, in the opinion of the Investigator, the AE places the patient at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization that occurs during the course of a patient's participation in a clinical study, except for those due to the following:
  - A surgery or procedure that was planned before the patient entered the study and which is part of the planned study procedure.
  - Nonmedical reasons (eg, elective hospitalization for social reasons or due to long travel distances or for prophylactic patient observation), in the absence of an AE.

  Note: "Inpatient hospitalization" means the patient has been admitted to a hospital for medical reasons.
- 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 (eg, a new cancer that is not a condition of the study indication or is a serious symptom of study drug overdose).

An efficacy failure is not considered an SAE. 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.

10.7 Serious AE Reporting

Serious AEs will follow the same monitoring process as referenced in Section 10.2; however, events occurring after the patient has provided informed consent, but before the first dose of study treatment or confirmed screen failure, will be collected as medical history unless the event is either new and attributed to protocol-mandated procedures by the Investigator or there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Any new or clinically significant changes in the patient's medical

and/or cancer history that occur after the first dose of drug and meet the SAE criteria will be recorded as SAEs. All SAEs meeting serious criteria, from the time of treatment randomization through 90 days after cessation of study treatment or 30 days after cessation of study treatment if the patient initiates new anticancer therapy, whichever is earlier, must be reported by the Investigator to Nektar Therapeutics Drug Safety immediately (ie, no more than 24 hours after learning of the event).

In addition, all SAEs that occur beyond 90 days after the last dose of all study drug(s) that are assessed by the Investigator as related to study drug(s) will also be reported to Nektar Therapeutics Drug Safety immediately without undue delay, under no circumstances later than 24 hours following knowledge of the event.

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline. 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.

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, that is, 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 provided in the List of Study Contacts 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.

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, AESI, or ECIs 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 10.8.

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.

10.8 Serious AE Follow-up

All study treatment-related SAEs that have not resolved by the last Follow-Up Visit (Section 6.3) will be followed until any of the following occur (whichever comes first):

- The event resolves.
- The event has stabilized.
- The event returns to baseline, if a baseline value is available.
- It is unlikely that any additional information can be obtained (eg, patient or healthcare practitioner refuses to provide additional information; lost to follow-up after demonstration of due diligence with follow-up efforts [as defined in Section 6.2.7]).
- The patient dies or is lost to follow-up (as defined in Section 6.2.7).

All ongoing SAEs assessed as unrelated to study drug(s) will be followed until resolution or until the last Follow-Up Visit (Section 6.3), whichever is earlier. In the case where an unrelated SAE has not completely resolved by the last Follow-Up Visit, the final outcome of these unrelated ongoing SAEs will be captured as “Not Recovered/Not Resolved” or “Recovering/Resolving”, whichever is applicable.

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

It is anticipated that during this study a proportion of patients will experience disease recurrence prior to study discontinuation. In some patients this may result in hospitalization or death. Such events leading to hospitalization or death of a study patient are typically considered “serious,” requiring submission of an SAE report. However, because disease recurrence is an endpoint for this study, reporting the term “disease recurrence” as either an AE or SAE is not necessary. Signs and symptoms with no principal clinical manifestation related to disease recurrence, may be considered as “disease recurrence” without a requirement to report it as an AE or SAE.

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

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

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

However, if there are separate identifiable clinical manifestations of the disease recurrence that the Investigator is unsure that the events are attributed solely to disease recurrence, for example, pleural effusion or weight loss, these manifestations are reportable as AEs. Such an event should be recorded on the AE CRF and, if the event meets any of the "serious" criteria, it must also be reported on the SAE form.

10.10 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the patients in the study.

10.11 Immune-Mediated Adverse Events

Immune-mediated AEs (also referred to as immune-related AEs [irAEs] in this document) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Investigators should use clinical judgment characterizing an AE as immune-mediated, including the requirement for steroid treatment, and are encouraged to rule out neoplastic, infectious, metabolic, toxic, or other etiologies to the extent possible, before characterizing an event as immune-mediated. Information supporting the assessment of immune-mediated AEs will be collected on the CRF.

10.12 Adverse Events of Special Interest for Bempegaldesleukin

Selected serious and nonserious AEs for bempegaldesleukin are also known as adverse events of special interest (AESIs) and must be reported to the Sponsor.

An AESI for bempegaldesleukin in this study is CVA, which should follow the AE grading criteria (see Section 10.3) and the standard seriousness definition (see Section 10.6). All AESIs occurring in both arms are required to follow the timeline for SAE reporting (within 24 hours as described in Table 11 and Section 10.7) in order to remove potential bias from dissimilar reporting between the treatment arms. The purpose of such reporting criteria is to obtain adequate information for proper clinical assessment of CVA events. Patients with recurrent and metastatic disease are known to have a higher risk for CVA.

CVA Management Guidelines for the study are provided in Appendix 2.

10.13 Potential Drug-Induced Liver Injury for Bempegaldesleukin

For patients in Arm A receiving bempegaldesleukin, wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event according to the elevated liver enzyme criteria defined in Section 10.14. For patients in Arm A receiving bempegaldesleukin, all occurrences of potential DILIs meeting the criteria defined in Section 10.14 must be assessed for causal etiology with concomitant medications and/or for individual study drug association and reported as SAEs (see Section 10.7 for reporting details).

10.14 Events of Clinical Interest for Pembrolizumab

Selected serious and nonserious AEs for pembrolizumab are also known as events of clinical interest (ECIs) and must be reported to the Sponsor.

Events of clinical interest for pembrolizumab in this study include:

1. An overdose of Sponsor's product, as defined in Section 10.15.

2. An elevated AST or ALT laboratory value that is greater than or equal to 3 × ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 × ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

10.15 Treatment of Overdose

For this study:

- For pembrolizumab, an overdose will be defined as any dose of 1000 mg pembrolizumab or greater.
- For bempegaldesleukin, an overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

No specific information is available on the treatment of overdose of pembrolizumab or bempegaldesleukin. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Section 10.6). All instances of accidental overdose and/or dosing errors should be reported on the Dosage Administration Record CRF.

10.16 Pregnancy Tests/Pregnancy

10.16.1 Pregnancy Tests

Serum or urine pregnancy tests will be performed on women of childbearing potential (WOCBP) according to the Schedule of Events (Section 1.2). Pregnancy testing (urine or serum as required by local regulations) should also be conducted 120 days after the last dose of study drug.

Pregnancy testing requirements for study inclusion are described in Section 5.1.

Pregnancy testing (urine or serum as required by local regulations) should be conducted prior to every cycle (q3w) or more frequently if required by local regulations.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Urine pregnancy tests should have a highly sensitive pregnancy test. A negative pregnancy test result must be obtained before the administration of the study drug(s).

A pregnancy test does not need to be performed on women who are postmenopausal (see Appendix 5) for at least 1 year or surgically sterile for at least 3 months before signing the ICF.

10.16.2 Pregnancy

10.16.2.1 Pregnancy and Lactation in Female Patients

The Sponsor must be notified immediately without undue delay, under no circumstances later than 24 hours following knowledge of the initial report and any follow-up reports of a female patient becoming pregnant or breastfeeding during the course of the study and for 120 days after the last dose of study drug or 30 days after cessation of study drug if the patient initiates a new anticancer treatment for female patients. All reports should be submitted via the Pregnancy Notification Form. Pregnancy, although reportable, is not considered an AE/SAE unless a female patient experiences signs or symptoms of pregnancy complications; however, the contact information for pregnancy reporting is the same as for SAE reporting and listed in Section 10.7. Female patient(s) who become pregnant will be followed until the outcome of the pregnancy is known. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring. Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

10.16.2.2 Arm A Only: Pregnancies in Female Partners of Male Patients

For patients treated with bempegaldesleukin, any pregnancy occurring during the course of the study and for 3 months after the last dose of bempegaldesleukin in a female partner of a male patient must be reported to the Sponsor. The Sponsor must be notified immediately without undue delay, under no circumstances later than 24 hours following knowledge of the initial report and any follow-up information. All reports should be submitted via the Pregnancy Notification Form. In order for the Sponsor or designee to collect any pregnancy surveillance information, the pregnant patient or partner must sign an informed consent form (See Section 14.2).

Pregnancy, although reportable, is not considered an AE/SAE unless a female partner of a male patient experiences signs or symptoms of pregnancy complications; however, the contact information for pregnancy reporting is the same as for SAE reporting and listed in Section 10.7. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug with the authorization from the pregnant partner. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring. Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

10.17 Emergency Medical Support and Patient Card

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

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

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected patient. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, he/she will answer any questions. Any subsequent action will follow the standard processes established for the Investigators. In cases where the Investigator is not available, the Sponsor will provide a 24-hour

contact number, whereby healthcare providers are given access to a physician designated by the Sponsor who can assist with the medical emergency.

10.18 Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Events (Section 1.2). A list of the clinical laboratory analytes to be tested is provided in Appendix 1.

Clinical laboratory tests will be performed by the central laboratory. For randomization, if the central laboratory tests are cancelled, lost, or considered inadequate for analysis, the site may forward an identical set of local laboratory samples for eligibility review (with central laboratory testing repeated prior to the first dose of study drug). If local laboratory results are determined to be acceptable during eligibility review, randomization may proceed. Additional clinical laboratory tests may be ordered at the Investigator's discretion.

The Investigator will review all laboratory results for clinical significance. Any laboratory result deemed clinically significant (ie, is associated with signs and symptoms, requires treatment, or requires follow up) will be recorded as an AE as described in Section 10.1.

10.19 Physical Examinations

Physical examinations should be conducted according to the Schedule of Events (Section 1.2).

Full physical examinations evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, and neurologic. Targeted physical examinations are at the discretion of the Investigator to identify changes from baseline or evaluate changes based on the patient's clinical symptoms.

10.20 Vital Signs

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

10.21 Electrocardiograms

All patients will have 12-lead electrocardiogram (ECG) done during Screening as specified in the Schedule of Events (Section 1.2). ECG data will be locally assessed. On-treatment ECGs should be obtained if clinically indicated.

10.22 Echocardiograms

Standard echocardiogram will be performed at screening to assess cardiac function and LVEF according to the Schedule of Events (Section 1.2). A MUGA scan can be performed to assess

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

11.0 STATISTICAL PLAN

11.1 General Considerations

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

All efficacy evaluations will be analyzed using the intent-to-treat (ITT) population unless otherwise specified, and all safety endpoints will be summarized using the Safety population. In general, the following three stratification factors will be used in stratified analysis in comparing response rates and survival curves of the two arms (bempegaldesleukin plus pembrolizumab versus pembrolizumab), and in Cox proportional hazard analysis unless otherwise specified: disease status (metastatic vs recurrent only), PD-L1 tumor expression (CPS ≥ 20 vs CPS 1-19) and HPV status (positive vs negative).

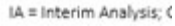
The detailed description of analysis methods will be provided in the statistical analysis plan (SAP).

11.2 Determination of Sample Size

The sample size of the study accounts for the following two primary efficacy endpoints: ORR and OS. The overall alpha for this study is 0.05, which is split into 0.001 to evaluate ORR and 0.049 to evaluate OS. All alpha levels are two-sided. At the first interim analysis (Interim Analysis 1 [IA1]), ORR will be analyzed at least one month after the last patient of the Phase 2 portion has been randomized into the study. IA2 will occur when at least 231 OS events have been observed. ORR and OS will be analyzed at IA2 for efficacy and OS will be analyzed for efficacy at the final analysis (FA).

In addition, a fallback approach will be used to reallocate the alpha from ORR to OS. If ORR is significant in favor of the combination of bempegaldesleukin and pembrolizumab, the alpha of 0.001 will be passed to OS. OS can then be tested at 0.05 (instead of 0.049) level. The testing procedure of ORR and OS is described in Figure 2. A total of approximately 500 patients will be randomized into the two treatment arms (bempegaldesleukin plus pembrolizumab versus pembrolizumab) in a 1:1 ratio.

Figure 2: Statistical Testing Procedure



Abbreviations: ~ = approximately; Δ = change; FA = final analysis; GNG = go no go decision; IA = interim analysis; IA1 = Interim Analysis 1 (first interim analysis); IA2 = Interim Analysis 2 (second interim analysis); mos. = months; ORR = objective response rate; OS = overall survival; p = p-value

11.2.1 Sample Size Justification for ORR

It is projected that IA1 will occur approximately 14 months after the first patient's randomization date (10 months of accrual of 200 patients in both arms, one month of ORR follow-up, and 3 months for data cleaning). IA1 is for ORR futility assessment.

Given a two-sided family-wise error rate of 0.001, 500 patients in the ITT population will provide approximately 96% power to detect a 20% difference in ORR between the 2 treatment arms using a Chi-square test at IA2, assuming an ORR of 19% for pembrolizumab (Burtness 2019). If the observed ORR difference at IA2 is greater than 13.1%, the result will be statistically significant.

11.2.2 Sample Size Justification for OS

The study is powered to detect an improvement in OS for bempegaldesleukin combined with pembrolizumab compared with pembrolizumab monotherapy. An initial total of 298 OS events are needed to detect a hazard ratio (HR) of 0.7 with 85% power at a 2-sided significance level of 0.049. Assuming a median OS time for the pembrolizumab arm of 12.3 months (Burtness 2019), with a total sample size of 500, it is projected the total study duration is up to 52 months to reach 393 OS events (after an initial varying staged incremental accrual in the first 5 months to 35 patients per month, then a 4-month enrollment pause after 200 patients have been randomized

and resumed at an initial varying staged incremental accrual in the first 3 months to 35 patients per month until 500 patients are randomized).

One interim analysis of OS is planned for this study at IA2. The interim analysis is projected to occur at 32 months from the first patient randomized into the study. The stopping boundaries at interim and final analyses will be derived based on the number of deaths using O'Brien and Fleming alpha spending function in software EAST 6.5. The detailed alpha spending and statistical significance level at each analysis below are for the planned number of events. If the actual number of events at the time of the analysis is different from the planned one, the actual alpha and statistical significance level will be adjusted using O'Brien and Fleming alpha spending function in software EAST 6.5.

There are two possible testing scenarios at IA2 for OS:

1. The ORR difference is statistically significant at IA2 at alpha level of 0.001.

   The overall Type I error rate is 0.05 for the primary endpoint OS and OS will be tested at alpha level of 0.022 at IA2. If the observed HR is tested statistically significant in favor of the combination of treatments, OS benefit will be concluded. Otherwise, OS will be tested at alpha level of 0.028 at the final analysis (FA) corresponding to the statistical significance level of 0.044 calculated based on the correlation of the interim and final combination test statistic.

2. The ORR difference is not statistically significant at IA2.

   The overall Type I error rate is 0.049 for the primary endpoint OS. OS will be tested at alpha level of 0.021 at IA2. If the observed HR is tested statistically significant in favor of the combination of treatments, then OS benefit will be concluded. Otherwise, the HR will be tested at alpha level of 0.029 at the final analysis corresponding to the statistical significance level of 0.043 calculated based on the correlation of the interim and final combination test statistic.

The detailed calculation will be provided in the SAP.

At IA2, if OS is not statistically significant, then conditional power will be calculated. The adaptive method in Liu and Hu (Liu 2016) and Mehta and Pocock (Mehta 2011) will be used to determine the number of OS events needed to target approximately 85% to 90% conditional power for the final analysis. The final analysis will be triggered when this re-estimated number of OS events is reached.

The minimum and maximum number of OS events for the final analysis are 298 and 393, respectively. The minimum event size is calculated to achieve 86% power with alpha = 0.049 (two-sided) assuming an exponential distribution in each treatment arm and an HR = 0.7 with median OS for the pembrolizumab arm of 12.3 months (Burtness 2019). The maximum event size is determined to detect the minimum clinically meaningful effect of HR around 0.82.

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

The key secondary endpoints will be tested hierarchically given statistical significance of OS. Further details of the testing procedure will be described in the SAP.

Figure 2 provides the study flow and decision-making time points for the primary endpoints.

11.3 Analysis Sets

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

Population	Description
ITT Population	All patients who are randomized. Patients are grouped within the ITT population according to the treatment to which they are randomized. This is the primary analysis set for baseline characteristics and efficacy endpoints unless otherwise specified.
Safety Population	All patients who receive ≥ 1 dose (or partial dose) of study drug. Patients are grouped according to the treatment they actually receive. This is the primary analysis set for all safety analyses and drug administration.
PK Population	All patients in the safety population who have evaluable analyte concentration-time profiles that allow for computation of meaningful PK parameter values.
Immunogenicity Population	All patients in the safety population with baseline and ≥ 1 post-baseline immunogenicity assessment.
[redacted]	[redacted]
HRQoL Population	All patients in the ITT population who have a baseline and ≥ 1 post-baseline assessment (defined for each instrument).

Abbreviations: HRQoL = health-related quality of life; ITT = intent-to-treat; PK = pharmacokinetic

11.4 Demographics and Baseline Characteristics

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

11.5 Efficacy Analyses

11.5.1 Primary Efficacy Analyses

ORR is defined as the percentage of patients with a confirmed best overall response of CR or PR by RECIST 1.1 per BICR in the ITT population. As a primary efficacy endpoint, ORR will be tested at an overall alpha level of 0.001. The Cochran Mantel Haenszel (CMH) test statistic will

be used to compare the proportion of patients with an objective response between the 2 treatment arms.

The ORR difference between the two treatment arms with its 95% and 99.5% confidence intervals (CIs) will be calculated by the CMH test statistic using the normal approximation. The ORR and its corresponding 95% exact CI will also be calculated by Clopper-Pearson method for each arm. Patients who do not have on-study tumor assessments to evaluate response status will be counted as non-responders.

Overall survival (OS) is defined as the time between the date of randomization and the date of death due to any cause. A patient who does not have a date of death will be censored on the last date for which the patient was known to be alive.

As another primary efficacy endpoint, OS will be evaluated at an overall alpha level of 0.049 if ORR is not significant and at 0.05 if ORR is significant. The regular stratified log-rank test will be used at IA2 to compare overall survival between the two treatment arms. At the final analysis, the weighted combination version of the stratified log-rank test with prespecified weights (Lehmacher 1999) will be used to compare overall survival between the two treatment arms. A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the hazard ratio and corresponding 95% CI. The weighted combination approaches as specified in Brannath et. al. (Brannath 2006) will be performed as an exploratory analysis. The Kaplan-Meier method will be used to summarize overall survival per arm, including Kaplan-Meier curves, medians with corresponding 95% CIs, etc.

At the first interim analysis, ORR will be assessed for futility: ORR futility assessment (ie, the difference in ORR proportions is ≥ 0% [bempegaldesleukin plus pembrolizumab minus pembrolizumab monotherapy]) will serve as a gate to proceed to the Phase 3 portion of the study.

If the DMC determines that the study should continue based on the prespecified futility boundary, Phase 3 of the study will begin following a projected 4-month enrollment pause for the first interim analysis readout. At the second interim analysis when approximately 500 patients have been randomized and about 231 overall survival events have been observed, the following tests will be conducted:

- ORR will be tested at a statistical significance level of 0.001 at the second interim analysis.
- If ORR is not significant at the second interim analysis, overall survival will be tested at an overall alpha level of 0.049 and at $\alpha = 0.021$ at the second interim analysis.
- If ORR is significant at the second interim analysis, the fallback method will be used, and overall survival will be tested at an overall alpha level of 0.05 and at $\alpha = 0.022$ at the second interim analysis.

At the final analysis, the primary analysis of overall survival to claim statistical significance will be based on the weighted combination version of the stratified log-rank test with prespecified

weights (Lehmacher 1999). Statistical significance level for the final analysis is 0.043 or 0.044 depending on whether ORR is significant at the second interim analysis. Prespecified weights for the primary OS are $w = \sqrt{231/345}$ and 1-w for events occurring before and after the second interim analysis, respectively. The middle point, 345, of minimum and maximum event sizes is chosen to set up the weights. The conventional stratified log-rank test with equal weights for every patient will be conducted as a sensitivity analysis. Details will be provided in the SAP.

11.5.2 Secondary Analyses

Progression-free survival (PFS): defined as the time between the date of randomization and the first date of documented disease progression using RECIST 1.1 per BICR or death due to any cause, whichever comes first. Stratified log-rank test will be used to compare PFS between the two treatment arms. PFS will be tested following OS significance and at the same significant level as OS. A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the hazard ratio and corresponding 95% CI for PFS. The Kaplan-Meier method will be used to summarize PFS, including Kaplan-Meier curves, medians with corresponding 95% CIs, etc.

The censoring rules for PFS will be detailed in the SAP.

[redacted]

11.6 Safety Analyses

Overall safety and tolerability of bempegaldesleukin plus pembrolizumab will be measured by the incidence of treatment emergent AEs including AEs of special interest, SAEs, deaths, and laboratory abnormalities. Safety analyses will be summarized for the Safety population using descriptive statistics by treatment arm.

11.7 Interim and Final Analyses

- IA1: at least one month after the last patient of the Phase 2 portion has been randomized into the study. It is projected that IA1 will occur approximately 14 months after the first patient's randomization date. The analysis is for futility based on ORR.
- IA2: after at least 231 OS events have been observed. The interim analysis is projected to occur at 32 months from the first patient randomized into the study. The analysis is for ORR for efficacy, for the first OS interim efficacy analysis, and for total number of OS events re-estimation if OS is not significant at IA2.
- FA – OS final: timing will be determined based on the IA2 efficacy results.

The SAP will further describe the planned interim analyses.

11.8 Data Monitoring Committee (DMC)

An independent, external DMC will be formed, comprised of qualified clinicians and a biostatistician all independent from the Sponsor and investigational sites, selected to avoid conflict(s) of interest.

The DMC will evaluate 2 interim analyses. The first interim futility analysis will occur at least one month after the last patient of the Phase 2 portion has been randomized into the study. The second interim efficacy analysis will be conducted when approximately 500 patients have been randomized and about 231 overall survival events have been observed.

The DMC will assess accumulating safety data and emerging risk/benefit balance at least twice a year and on an ad-hoc basis as detailed in the DMC Charter.

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

[redacted]

11.9.1 Pharmacokinetic Analyses

Plasma concentrations of bempegaldesleukin-related molecules and serum concentrations of pembrolizumab will be measured using validated or qualified method(s).

PK concentrations will be summarized using summary statistics. PK concentrations from this study will be combined with data from other studies to conduct population PK analyses. Model predicted exposures may be used for exposure-response analyses of selected efficacy and safety endpoints. If the analyses are conducted, the results of population PK analyses and exposure-response analyses will be reported separately from the Clinical Study Report of this study.

11.9.2 Immunogenicity Analyses

Incidence of anti-drug antibodies (ADA) will be determined by measurements of anti-bempegaldesleukin, anti-interleukin-2 (anti-IL-2), anti-polyethylene glycol, and anti-pembrolizumab antibodies. Validated methods will be used for the ADA measurements. Immunogenicity will be reported for ADA positive status and ADA negative status, relative to baseline. Presence of neutralizing antibody may be reported, if applicable. Effect of immunogenicity on safety/efficacy and PK may be explored.

11.9.3 Patient-reported Outcome Analyses

Patient-reported outcome (PRO) questionnaires, EORTC QLQ-C30 and EORTC QLQ-H&N35, will be administered by trained site personnel and completed by patients at baseline and throughout the study. It is a best practice and strongly recommended that PROs are administered to randomized patients prior to study drug administration, AE evaluation, and disease status notification.

Global health status/quality of life assessment is based on the global health status/quality of life scales of the EORTC QLQ-C30 (items 29 and 40); pain is based on the pain multi-item scales of the EORTC QLQ-H&N35 (items 31 to 34), and time to deterioration in swallowing (ie, the time from baseline to first onset of PRO deterioration with confirmation), is based on the swallowing multi-item scales of the EORTC QLQ-H&N35 (items 35 and 38). The deterioration in the global health status/quality of life, pain, and swallowing endpoints is defined as a 10 points or greater worsening from baseline for each multi-item scale (Bjordal 2000; Osoba 1998; King 1996) and confirmed by a second adjacent 10 points or more deterioration from baseline under a right-censoring rule.

Time to PRO deterioration in global health status/quality of life: defined as time from baseline to the first onset of PRO deterioration with confirmation at the next visit for the global health status/quality of life assessment based on the global health status/quality of life scales of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30).

Time to PRO deterioration in pain: defined as time from baseline to the first onset of PRO deterioration with confirmation for pain based on the pain multi-item scales of EORTC QLQ head and neck cancer specific module (EORTC QLQ-H&N35).

Time to PRO deterioration in swallowing: defined as time from baseline to the first onset of PRO deterioration with confirmation for swallowing based on the swallowing multi-item scales of EORTC QLQ-H&N35.

For the above three time to PRO deterioration endpoints, the stratified log-rank test will be used to compare the two treatment arms. A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the hazard ratio and corresponding 95% CI, and the Kaplan-Meier method will be used to summarize these time-to-event endpoints per arm, including Kaplan-Meier curves, medians with corresponding 95% CIs, etc.

Mean change from baseline in global health status/quality of life: defined as mean changes from baseline in global health status/quality of life assessment based on the global health status/quality of life scales of EORTC QLQ-C30.

To assess the treatment effects on the PRO score changes from baseline in the global health status/quality of life outcome, a constrained longitudinal data analysis (cLDA) model will be applied, with the PRO score as the response variable, and treatment by time interaction, and stratification factors as covariates. Treatment effect on PRO score change from baseline will be primarily evaluated at Week 12. The differences in the least square mean change from baseline will be reported at the primary analysis time point.

Additionally, mean change from baseline in global health status/quality of life will be summarized by visit and the graphs for the mean changes across visits will be provided.

Changes from baseline in HR-QoL assessments: Change from baseline in health-related quality-of-life (HR-QoL) assessed by EORTC QLQ-C30 and the EORTC QLQ-H&N35 will be summarized by visit and graphs for mean changes by visit will be provided.

Opioid analgesic use: will be measured based on reported concomitant medications. Opioid analgesic use will be summarized descriptively and the mean opioid analgesic use and change from baseline will be plotted across visits.

12.0 STUDY OR STUDY SITE TERMINATION

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

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

13.0 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.

13.1 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 submitted to applicable local health authorities, 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.

13.2 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 electronic case report forms (eCRFs), study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR 312 Subpart D (Responsibilities of Sponsors and Investigators), ICH GCP, and local regulations, the monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs; ensure that all protocol requirements, applicable FDA, ICH GCP, and local regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) for the patients in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor. The Investigational New Drug (IND) Application regulations and ICH E6 guidelines also require the Investigator to allow authorized representatives of the Sponsor, IRB/IEC, FDA, and other relevant regulatory authorities direct access to study source records, and to inspect and make copies of the same records. The names and identities of the patients need not be divulged to the Sponsor; however, the records must nevertheless be available to be inspected for review. This can be accomplished by blacking out the patient's name and replacing the name with the patient's study identification number. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the Investigator must inform the Sponsor of these restrictions before initiation of the study.

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

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

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

14.0 ETHICAL CONSIDERATIONS

This study will be conducted to be consistent with the principles that have their origin in Declaration of Helsinki and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with the current ICH GCP guidelines (ICH E6), as well as with any applicable regulatory authority, federal, state and/or local laws and regulations.

14.1 IRB/IEC Approval

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

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

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

14.2 Written Informed Consent

Written documentation of informed consent must be obtained from each patient or (if permitted by the local health authority) a patient's legal representative before entering the study. Patients will be informed of the nature of the study, and the ICF must be presented to each patient in the language in which the patient is fluent.

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

Any pregnancy that occurs in a study patient or the female partner of a male study patient should be reported to the Sponsor or designee. For the Sponsor or designee to collect any pregnancy surveillance information, the pregnant patient or partner must sign an informed consent form for disclosure information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

15.0 DATA HANDLING AND RECORD KEEPING

15.1 Data Collection Instruments and Source Documents

15.1.1 Study Records

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

15.1.2 Data Collection Instruments

Data collection instruments (DCIs) (eg, eCRFs, electronic clinical outcomes assessments, and/or 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.

15.2 Retention of Essential Documents

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

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

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

15.3 Confidentiality

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

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

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

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

15.4 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.

16.0 PUBLICATION PLAN

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

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

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

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APPENDIX 1: CLINICAL LABORATORY TESTS

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

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

Appendix 1A: Laboratory Tests Performed in This Study

<table>
<tr><th colspan="3">Clinical Laboratory Tests (Central Laboratory)</th></tr>
<tr><th>Hematology</th><th>Chemistry</th><th>Serology (screening only)</th></tr>
<tr><td>• Hemoglobin (Hgb)
• Hematocrit (HCT)
• Platelet count
• White blood cell (WBC) count
• Absolute neutrophil count
• Absolute lymphocyte count
• Monocytes
• Eosinophils
• Basophils</td><td>• AST (SGOT)
• ALT (SGPT)
• Alkaline phosphatase (ALP)
• Albumin
• Creatinine
• Calculated creatinine clearance
• Calcium
• Glucose (non-fasting)
• Total protein
• Total bilirubin
• Direct bilirubin
• Sodium
• Potassium
• Chloride
• Carbon dioxide (CO_2) or bicarbonate
• Blood urea nitrogen (BUN) or serum urea
• Lactate dehydrogenase (LDH)
• Uric acid</td><td>• Hepatitis B surface antigen (HBsAg)
• Hepatitis C virus antibody (anti-HCV)
• Human immunodeficiency virus (HIV) antibody</td></tr>
<tr><th>Thyroid Function Tests</th><th>Coagulation</th><th>Additional Labs</th></tr>
<tr><td>• Free or total triiodothyronine (T3)
• Free thyroxine (T4)
• Thyroid-stimulating hormone (TSH)</td><td>• Activated partial thromboplastin time (aPTT)
• Prothrombin time (PT)
• International normalized ratio (INR)</td><td>• Creatine kinase
• Lipase
• Amylase
• Serum or urine pregnancy
• ***For females < 55 years of age***: Follicle-stimulating hormone (FSH)</td></tr>
<tr><th colspan="3">Urinalysis</th></tr>
<tr><td colspan="3">• Specific gravity
• pH
• Glucose
• Protein
• Bilirubin
• Ketones
• Leukocyte esterase
• Blood

For positive protein, white blood cell, or blood: perform a microscopic examination including:
• Red blood cells
• White blood cells
• Epithelial cells
• Bacteria
• Crystals
• Casts</td></tr>
</table>

Abbreviations: ALT = alanine transaminase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate transaminase (serum glutamic oxaloacetic transaminase)

Appendix 1B. Arm A Only: Local Clinical Laboratory Tests Obtained Prior to Bempegaldesleukin Administration

Laboratory Tests Required for Arm A Treatment Decision		
• AST (SGOT) • ALT (SGPT) • Serum creatinine • Blood urea nitrogen (BUN)	• Total bilirubin • Sodium • Potassium	• Pregnancy test (for WOCBP, see Appendix 5) • Any additional clinically-relevant test related to individual patient monitoring

Abbreviations: ALT = alanine transaminase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate transaminase (serum glutamic oxaloacetic transaminase); WOCBP = women of childbearing potential

Local laboratory tests must be assessed within 24 hours, or as soon as locally feasible, prior to each administration of bempegaldesleukin.

APPENDIX 2: CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM FOR PATIENTS IN ARM A RECEIVING BEMPEGALDESLEUKIN

If a new event of CVA including TIA occurs during the study conduct, please assess all etiologies of thrombo-embolic causes in these high-risk patients with known hypercoagulable state in the advanced cancer setting.

The table below provides a management algorithm for possible signs/symptoms of CVA for patients in Arm A receiving bempegaldesleukin. This general guideline constitutes guidance to the Investigator and may be supplemented by clinical judgment of the Investigator and/or discussions with the Medical Monitor representing the Sponsor.

For unexplained neurological symptoms (such as hemiparesis, confusion, dysarthria, or visual disturbances) that may be associated with CVA: • Recommend following the Advanced Cardiac Life Support (ACLS; ACLS 2021) Adult Suspected Stroke Algorithm (that includes time-sensitive assessment and rtPA use guidance). • Perform neurological imaging with DWI MRI as soon as feasible after initial presentation of symptoms, preferably within 24 hours, or as indicated following acute intervention. DWI MRI is preferred, but if contraindicated, alternative imaging modalities may be used. If imaging is consistent with a CVA, proceed to the following:	
1	For any new CVA events confirmed by imaging (DWI MRI preferred unless contraindicated), regardless of neurological symptoms (eg, cryptogenic CVA) and for suspected TIA without clear alternative etiology: • Discontinue bempegaldesleukin. After a careful risk-benefit evaluation of each patient and if the CVA/TIA event is not deemed related to the checkpoint inhibitor, pembrolizumab may be continued.
2	Obtain a neurology consultation
3	Perform laboratory assessments (including coagulation studies with D-dimer, complete blood count [CBC] with differential, serum blood urea nitrogen [BUN], and creatinine).
4	Consider cardiac echocardiogram (trans-esophageal as appropriate) to evaluate for potential source of emboli.

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

Note: The ACLS Adult Suspected Stroke Algorithm is available from: https://acls-algorithms.com/adult-stroke-algorithm/.

APPENDIX 3: PERFORMANCE STATUS CRITERIA

GRADE	ECOG PERFORMANCE 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, for example, light housework, 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

Abbreviation: ECOG = Eastern Cooperative Oncology Group

Oken 1982

APPENDIX 4: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) (VERSION 1.1) FOR EVALUATING RESPONSE IN SOLID TUMORS

RECIST version 1.1 (Eisenhauer 2009) will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

APPENDIX 5: WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Women of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PATIENTS OF CHILDBEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 120 days after the last dose of study treatment (Note: local laws and regulations may require use of alternative and/or additional contraception methods).

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*[a]
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • oral • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Hormonal methods of contraception including vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP patients who choose complete abstinence must continue to have pregnancy tests, as specified in Section 1.2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP patients chooses to forego complete abstinence
NOTES: a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies. b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the investigational medicinal product (IMP) and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. c. Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.

Unacceptable Methods of Contraception[a]
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • Lactation amenorrhea method (LAM)

a. Local laws and regulations may require use of alternative and/or additional contraception methods.

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

For Arm A (bempegaldesleukin plus pembrolizumab): male patients with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

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

For Arm B (pembrolizumab monotherapy): For male patients receiving pembrolizumab monotherapy, there are no contraception requirements.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information is provided in Section 10.16.

APPENDIX 6: CYTOKINE-RELEASE SYNDROME (CRS) MANAGEMENT MEASURES/ALGORITHM FOR PATIENTS IN ARM A RECEIVING BEMPEGALDESLEUKIN

The following treatment management guideline is provided for general guidance for patients in Arm A receiving bempegaldesleukin. Cytokine-release syndrome (CRS) is a diagnosis of exclusion. This guideline should not substitute for a more individualized, tailored approach to managing a patient experiencing CRS.

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

For patients with suspected CRS:

- For Grade 1 or Grade 2 events, implement supportive care, including management of isolated symptoms based on institutional practices
- Consider admitting the patient for monitoring and to provide supportive care, including management of isolated symptoms based on institutional practices and protocol management guideline (eg, hydration management guidelines in Section 6.2.3.2).
- For patients with a persistent or worsening clinical condition after initial treatment of CRS, re-evaluate for other contributing conditions. It is particularly important to reassess the patient for coexisting infections, cardiac, pulmonary, thromboembolic, and other complications.

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

Abbreviations: ICU = intensive care unit; O_2 = oxygen; PO = by mouth