Nektar Therapeutics

CLINICAL PROTOCOL

Protocol Number:	20-214-29/CA045-022
Title:	A Phase 3, Randomized, Open-label Study to Compare Adjuvant Immunotherapy of Bempegaldesleukin Combined with Nivolumab Versus Nivolumab After Complete Resection of Melanoma in Patients at High Risk for Recurrence (PIVOT-12)
Version:	Amendment 1.0
Date:	14 June 2021
Supersedes:	Amendment 0.1 dated 29 September 2020 (UK) Original Protocol dated 27 April 2020
US IND No.:	125471
Eudra CT No.:	2020-000917-34
Investigational Products:	bempegaldesleukin (NKTR-214) in combination with nivolumab
Indication:	Resected Stage IIIA (lymph node metastasis > 1 mm)/B/C/D and IV melanoma with no evidence of disease
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA
Sponsor's Medical Contact and Study Medical Monitor:	[redacted]

CONFIDENTIALITY STATEMENT

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

PRINCIPAL INVESTIGATOR COMMITMENT

Protocol Number:	20-214-29/CA045-022
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Version, Date:	Amendment 1.0, 14 June 2021
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

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

Principal Investigator Signature	**Date**

Printed Name: _____

Institution: _____

Address _____

PROTOCOL APPROVAL PAGE

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[redacted]

Signing Reason: I approve this document
Signing Time: Jun-18-2021 | 2:35:23 PM PDT
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Signature

Printed Name: [redacted]

LIST OF STUDY CONTACTS

Study Contact	Name	Contact Information
Nektar Medical Monitor	[redacted]	[redacted]
Associate Director, Clinical Development	[redacted]	[redacted]
Serious AE and Pregnancy Reporting	[redacted]	[redacted]

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ABBREVIATIONS

Abbreviation or Term	Definition
ACE	angiotensin converting enzyme
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	area under the drug concentration-time curve
bempegaldesleukin	International Nonproprietary Name (INN) for NKTR-214
BICR	blinded independent central review
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CRC	colorectal carcinoma
CRF	case report form
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
DMFS	distant metastasis-free survival
DOAC	direct oral anticoagulation
ECG	electrocardiogram
eCRF	electronic case report form

Abbreviation or Term	Definition
EORTC QLQ-C30	30-item European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire
EQ-5D-5L	European Quality of Life – 5 Dimensions Health State Classifier to 5 Levels
eSAE	electronic serious adverse event
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FPFV	first patient first visit
GCP	Good Clinical Practice
GH/QoL	global health/quality of life
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IFN-γ	interferon-γ
IL-2	interleukin-2. *For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule.*
IL-2Rβγ	IL-2 receptor beta gamma
IND	Investigational New Drug application
INR	international normalized ratio
IRB	institutional review board
IRT	Interactive Response Technology
ITT	intent-to-treat
IV	intravenous
kg	kilogram
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
LN	lymph node
LVEF	left ventricular ejection fraction
mg	milligram

Abbreviation or Term	Definition
min	minute(s)
mL	milliliter
MMIS	malignant melanoma in situ
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NED	no evidence of disease
NKTR-214	bempegaldesleukin (International Nonproprietary Name [INN] for NKTR-214)
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PEG	polyethylene glycol
PET	positron emission tomography
PK	pharmacokinetic
PPK	population pharmacokinetic
PROs	patient-reported outcomes
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
QoL	quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	recurrence-free survival
rhIL-2	recombinant human interleukin-2
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
TIA	transient ischemic attack

Abbreviation or Term	Definition
TME	tumor microenvironment
Tregs	regulatory T cells
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

1.0 STUDY SYNOPSIS

Title of Study:	A Phase 3, Randomized, Open-label Study to Compare Adjuvant Immunotherapy of Bempegaldesleukin Combined with Nivolumab Versus Nivolumab After Complete Resection of Melanoma in Patients at High Risk for Recurrence (PIVOT-12)
Sponsor:	Nektar Therapeutics
Name of Finished Product(s):	Bempegaldesleukin (NKTR-214 drug product) Opdivo®
Name of Active Ingredient(s):	Bempegaldesleukin (NKTR-214) drug substance Nivolumab (anti-programmed cell death protein 1 [PD-1] antibody)
Phase of Development:	Phase 3
Objectives:	The primary objective is to compare the efficacy, as measured by recurrence-free survival (RFS) by blinded independent central review (BICR), of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (lymph node [LN] metastasis > 1 mm), Stage IIIB/C/D, or Stage IV (American Joint Committee on Cancer [AJCC] 8th edition) cutaneous melanoma with no evidence of disease (NED) who are at high risk for recurrence. The secondary objectives are: • To compare the overall survival (OS) of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (LN metastasis > 1 mm), Stage IIIB/C/D, or Stage IV NED melanoma • To evaluate distant metastasis-free survival (DMFS) by BICR and by Investigator in patients who have Stage IIIA (LN metastasis > 1 mm) or IIIB/C/D melanoma at study entry • To evaluate time to disease progression after the next line of treatment for study patients following discontinuation of bempegaldesleukin plus nivolumab versus nivolumab • To assess the overall safety and tolerability of bempegaldesleukin plus nivolumab versus nivolumab in study patients • To describe changes in patient-reported outcomes (PROs) as assessed by the global health/quality of life (GH/QoL) and physical functioning subscales of the 30-item European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) • To evaluate the association between programmed cell death ligand 1 (PD-L1) expression status and RFS by BICR • To assess the efficacy, as measured by RFS by Investigator, of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (LN metastasis > 1 mm), Stage IIIB/C/D, or Stage IV NED melanoma [redacted]
Duration of Treatment:	Patients will be treated up to approximately 1 year (maximum of 17 cycles for Arm A and 13 cycles for Arm B) or until disease recurrence, death, unacceptable toxicity, symptomatic deterioration, decision by Investigator to discontinue treatment, decision by patient to discontinue treatment or withdraw consent from the study, patient is lost to follow-up, or decision by Sponsor to terminate the trial, whichever is earlier.
Study Population:	Patients aged 12 years and older with resected Stage IIIA (LN metastasis > 1 mm), Stage IIIB/C/D, or Stage IV NED melanoma

Number of Patients (Planned):	Approximately 950 patients
Study Design:	This is a multicenter, randomized, open-label, Phase 3 study that will evaluate the efficacy and safety of bempegaldesleukin plus nivolumab compared with nivolumab after complete resection of melanoma in patients at high risk for recurrence. Patients will be randomized in a 1:1 ratio to one of two treatment arms: • Arm A: bempegaldesleukin plus nivolumab every 3 weeks (q3w) • Arm B: nivolumab monotherapy every 4 weeks (q4w) Randomization will be stratified by: • PD-L1 status by Dako PD-L1 PharmDx 28-8 assay: PD-L1 ≥ 1% vs PD-L1 < 1% vs indeterminate/not evaluable Note: PD-L1 indeterminate/not evaluable will be capped at a maximum of 25% of the total patient population • Stage: IIIA(LN metastases > 1 mm)/IIIB vs IIIC vs IIID/IV Patients will be treated for approximately 1 year (maximum of 17 cycles for Arm A and 13 cycles for Arm B) or until disease recurrence, death, unacceptable toxicity, symptomatic deterioration, decision by Investigator to discontinue treatment, decision by patient to discontinue treatment or withdraw consent from the study, patient is lost to follow-up, or decision by Sponsor to terminate the trial, whichever is earlier. Efficacy, safety, pharmacokinetic (PK), immunogenicity, and biomarker assessments will be performed during treatment as presented in the On-Treatment Schedules of Events (Table 2 for Arm A; Table 3 for Arm B). Patients will undergo Safety Follow-up Visits for 100 (± 7) days after the last dose of study treatment and imaging assessments for up to 5 years from randomization (Table 4). Patients will be followed for survival until death, the patient withdraws consent from all further study assessments including survival follow-up, the patient is lost to follow-up, or the study is terminated by the Sponsor. The study will be considered complete when the last patient's last visit has been conducted and the data is mature for the final OS analysis (see Section 5.6).
Key Eligibility Criteria:	The following list contains key eligibility criteria only; a full list of eligibility criteria is provided in Section 4.0. **Key Inclusion Criteria:** • Male or female patients, ≥ 12 years of age at the time of signing the informed consent form, except where local regulations, countries, and/or institutional policies do not allow for patients < 18 years of age (adolescents) to participate. In regions where adolescents are not allowed to participate in the study due to age restrictions, enrolled patients must be ≥ 18 years of age. • Histologically confirmed Stage IIIA (LN metastasis > 1 mm [i.e., at least one LN metastasis measuring > 1 mm at greatest diameter]), IIIB/C/D, or IV (M1a/b/c/d) cutaneous melanoma by AJCC (8th edition) at study entry. o Patient must be completely surgically resected within 12 weeks prior to randomization. o Patients with in-transit or microsatellite disease will be allowed if disease has been completely surgically resected. o Patients must have been surgically rendered free of disease with negative surgical margins documented, as applicable. Please refer to Section 5.2 for details of minimum documentation requirements and Appendix 2 for AJCC 8th edition definitions of TNM and staging.

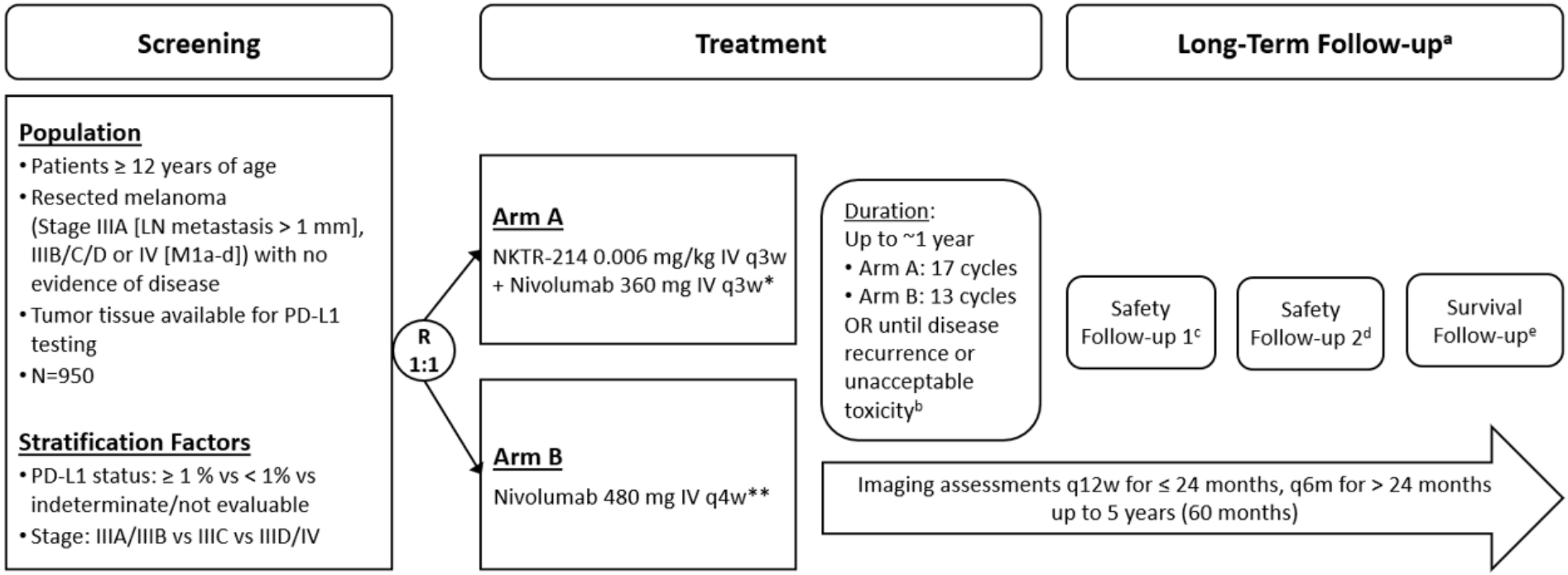
	• Tumor tissue available from biopsy or resected disease must be provided to central laboratory for biomarker and PD-L1 status analysis. Must have PD-L1 expression classification (≥ 1%, < 1%, indeterminate, or not evaluable) prior to randomization. • Disease-free status documented by a complete physical examination and imaging studies within 28 days prior to randomization (see Table 1 for details of required assessments). **Key Exclusion Criteria**: • History of ocular/uveal melanoma or mucosal melanoma. • Active, known or suspected autoimmune disease. Patients with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. • Conditions requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. • Prior therapy for melanoma except surgery for the melanoma lesion(s) and/or adjuvant radiation therapy for central nervous system lesions. • Prior therapy with interferon, talimogene laherparepvec (Imlygic®), interleukin-2 (IL-2) directed therapy, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T lymphocyte-associated protein 4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways). • Prior malignancy active within the previous 3 years except for locally potentially curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast. Consult with the Medical Monitor about prior melanoma or other potential exceptions.
Test Product, Dose and Mode of Administration:	• Bempegaldesleukin 0.006 mg/kg intravenous (IV) infusion q3w plus • Nivolumab 360 mg IV infusion q3w (or 4.5 mg/kg IV infusion q3w for patients < 40 kg)
Comparator Product, Dose and Mode of Administration:	• Nivolumab 480 mg IV infusion q4w (or 6.0 mg/kg IV infusion q4w for patients < 40 kg)
Biomarkers:	Tumor tissue will be collected pretreatment for characterization of PD-L1 status, [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, serum concentrations of nivolumab, as well as analytes for immunogenicity. PK parameters will be estimated from plasma or serum concentration-time data where possible. Incidence of anti-bempegaldesleukin, anti-IL-2, and anti-polyethylene glycol antibodies as well as incidence of anti-drug antibodies (ADA) to nivolumab will be evaluated.

	Immunogenicity will be reported for ADA positive status and ADA negative status, relative to baseline. In addition, presence of neutralizing antibody may be reported, if applicable.
Imaging Assessments:	Imaging assessments to assess patients for RFS will include: • Contrast-enhanced computed tomography (CT) of the chest; contrast-enhanced CT or magnetic resonance imaging (MRI) of the abdomen and pelvis; and all known sites of resected disease • Brain MRI (without and with contrast; head CT with contrast allowed in some cases [see Section 7.3 for details]) • Ultrasound of sentinel-node basin Imaging assessments will be performed up to the end of 5 years following randomization until investigator-assessed and BICR-confirmed distant recurrence (see Section 1.2 and Section 7.0 for further details).
Safety Evaluation:	Assessment of safety will be determined by an ongoing review of the following: • Adverse events (AEs), including treatment-emergent AEs, incidence of treatment-related AEs, serious AEs (SAEs), 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. **Analysis Populations**: • Intent-to-Treat (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. • Safety Population: All patients who receive at least 1 dose (or partial dose) of study drug. Patients are grouped according to the treatment they actually received. 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 treated patients with baseline and at least 1 post-baseline immunogenicity assessment. • Biomarker Population: All randomized patients who have biomarker data available at baseline. For pharmacodynamic biomarkers, the biomarker population includes all randomized patients who have baseline and at least one post-baseline biomarker data available. • Health-Related Quality of Life Population: All patients in the ITT population who had a baseline and at least 1 post-baseline assessment (defined for each instrument). **Efficacy:** The primary endpoint of RFS by BICR in the ITT population will be programmatically determined based on the disease recurrence date provided by BICR and is defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis by BICR), new primary melanoma (by

	BICR), or all-cause death, whichever occurs first. A log-rank test stratified by Stage and PD-L1 status will be used to compare RFS between the two treatment arms at an overall alpha level of 0.05 (two-sided). 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 RFS, including Kaplan-Meier curves, medians with corresponding 95% CIs, and RFS rates at 6, 12, 18, 24, and every 12 months thereafter with 95% CIs. Secondary endpoints will be assessed as follows: • OS, defined as the time between the date of randomization and the date of death due to any cause, will be tested at 0.05 alpha level when the follow-up time is at least 5 years for all patients if the primary analysis of RFS by BICR is significant, using a two-sided log-rank test stratified by randomization stratification factors. A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the hazard ratio and corresponding 95% CI. The Kaplan-Meier method will be used to further summarize OS rates at 6, 12, 18, 24, and every 12 months thereafter with 95% CIs. • DMFS by BICR, defined as the time between the date of randomization and the date of first distant metastasis by BICR or date of death due to any cause, whichever occurs first, will be evaluated in patients who are Stage III at study entry. • DMFS by Investigator, defined as the time between the date of randomization and the date of first distant metastasis by Investigator or date of death due to any cause, whichever occurs first, will be evaluated in patients who are Stage III at study entry. • Progression-free survival after the next line of treatment (PFS2), defined as the time from randomization to progression per Investigator after the start of next line of therapy or death, whichever occurs first, will be analyzed similarly to OS without formal testing. • PROs will be measured by changes from baseline in scores for the GH/QoL and physical functioning subscales of the EORTC QLQ-C30 questionnaire. • The predictive strength of PD-L1 expression as a biomarker will be measured by the endpoint RFS by BICR based on PD-L1 expression level using a Cox proportional hazards model to test the interaction between PD-L1 expression (≥ 1% vs < 1%) and treatment arm for the RFS endpoints. RFS will also be analyzed within each PD-L1 expression subgroup including log-rank tests and hazard ratios with corresponding CIs. The Kaplan-Meier method will be used to further summarize RFS in each subgroup at 6, 12, 18, 24, and every 12 months thereafter. The analyses will be descriptive. • RFS by Investigator will be measured similarly to the primary endpoint, but recurrence and new primary melanoma will be decided by the Investigator. [redacted] **Safety:** Overall safety and tolerability of bempegaldesleukin plus nivolumab will be measured by the incidence of AEs, SAEs, deaths, and laboratory abnormalities. Safety analyses will be performed in the Safety Population.

1.1 Study Schematic

Figure 1: Study Schematic



IV (when referring to treatment dose) = intravenous; LN = lymph node; NKTR-214 = bempegaldesleukin; PD-L1 = programmed cell death ligand 1; q3w = every 3 weeks; q4w = every 4 weeks; q6m = every 6 months; q12w = every 12 weeks.

a. Patients will undergo Safety Follow-up Visits for 100 (± 7) days after the last dose of study treatment and imaging assessments for up to 5 years from randomization.

b. See Section 5.3 for other protocol-defined reasons for treatment discontinuation.

c. Safety Follow-up 1: 30 (± 7) days after the last dose of all study treatment(s).

d. Safety Follow-up 2: 100 (± 7) days after the last dose of all study treatment(s).

e. Survival Follow-up: q12w (± 14 days) following the Safety Follow-up Visit 2 (or 100 [± 7] days after last dose of study treatment).

* Nivolumab 4.5 mg/kg IV q3w for patients < 40 kg.

** Nivolumab 6.0 mg/kg IV q4w for patients < 40 kg.

1.2 Schedule of Events

Table 1: Screening Schedule of Events

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Register in IRT system to obtain patient number. Must occur prior to any protocol-specific study assessments
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization
Medical History	X	Assessment of signs and symptoms and all medical history, including smoking history and alcohol use
Cancer History	X	Summary of melanoma cancer history, including prior treatment and BRAF mutation status (local results, if available)
Review of Pathology Report and Staging	X	Investigator documents staging and complete resection of disease (complete resection must be performed within 12 weeks prior to randomization) and provides pathology report for Sponsor review (refer to Inclusion Criterion No. 4 in Section 4.1)
Imaging Assessments	X	**Within 28 days prior to randomization** (see Section 7.3) Contrast-enhanced CT of the chest; contrast-enhanced CT or MRI of the abdomen, and pelvis and all known sites of resected disease Brain MRI (without and with contrast) (head CT with contrast allowed if MRI contraindicated and if there is no known history of treated brain lesions) Ultrasound of sentinel-node basin
Tumor Tissue Sample	X	Tumor tissue from biopsy or resected disease must be available and sent to a central laboratory: formalin-fixed paraffin-embedded block or unstained slides. Central PD-L1 classification (≥ 1%, < 1%, indeterminate, or not evaluable) required for randomization. Please refer to Section 5.8.1 for further details.

Procedure	Screening Visit	Notes
Safety Assessments		
Full Physical Examination	X	**Within 14 days prior to randomization** (see Section 8.17)
Vital Signs	X	**Within 14 days prior to randomization** Blood pressure, pulse, respiratory rate, temperature, pulse oximetry, height, and weight (see Section 8.18)
Performance Status	X	**Within 14 days prior to randomization** (see Appendix 3)
Prior and Concomitant Medication Use	X	**Within 14 days prior to randomization** (see Section 5.13) Document vaccine use within 30 days prior to randomization
Clinical Laboratory Testing	X	**Within 14 days prior to randomization** Laboratory assessment of hematology, chemistry, urinalysis, and serology (see Appendix 1)
Pregnancy Test	X	**Within 14 days prior to randomization** (see Section 8.13) Serum or urine test (minimum sensitivity 25 IU/L or equivalent units of HCG) in WOCBP
ECG	X	**Within 14 days prior to randomization** (see Section 8.19)
Echocardiogram or MUGA	X	**Within 60 days prior to randomization** (see Section 8.20)
EORTC QLQ-C30	X	**Within 14 days prior to randomization** (see Section 7.4.1) Performed for those ≥ 18 years of age at the time of informed consent and before any other study-related procedures
Randomization		
Randomization in IRT	X	Patient should be dosed within 5 calendar days following randomization

CT = computed tomography; ECG = electrocardiogram; EORTC QLQ-C30 = 30-item European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; HCG = human chorionic gonadotropin; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PD-L1 = programmed cell death ligand 1; WOCBP = women of childbearing potential.

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

Procedure[a]	Arm A Bempegaldesleukin (NKTR-214) and Nivolumab Cycle = 3 Weeks (21 days)						Notes
	Cycle 1				Cycles 2-17		
	Day 1 (≤ 5 days post-randomization)	Day 3 (-1 day)	Day 5 (± 1 day)	Day 8 (± 1 day)	Day 1 (± 3 days)	Day 4 (± 1 day) (call or visit)	
Study Drug and Hydration Follow-up							
Study Drug Administration	X				X		Dispense and administer study drugs following all predose assessments. Following first dose, subsequent doses of study drug may be administered no less than 18 days after prior dose of study drug. After the bempegaldesleukin infusion is administered, flush the IV line with an appropriate amount of diluent. If needed, flush the IV line with an appropriate amount of diluent after the nivolumab infusion. Refer to Section 5.3.2 and Pharmacy Manual for details.
IV Hydration and Review Oral Hydration Guidelines with Patient	X				X		Applicable only when bempegaldesleukin is administered. May be withheld if deemed in the best interest of the patient by the Investigator. Refer to Section 5.3.3.2 for further details.
Oral Hydration Follow-up		X^1				$X^{1,2}$	X^1 = For Cycle 1 and Cycle 2, site personnel must contact the patient (by telephone or clinic visit) at least once between Days 3 and 5, inclusive, to remind the patient of the oral hydration guidelines, to assess for any symptomatology and compliance with hydration guidelines, and document the results of the discussion (Section 5.3.3.2). X^2 = For Cycles 3 to 17, oral hydration follow-up should be conducted as clinically indicated between Days 3 and 5, inclusive.

Procedure[a]	Arm A Bempegaldesleukin (NKTR-214) and Nivolumab Cycle = 3 Weeks (21 days) Cycle 1 Day 1 (≤ 5 days post-randomization)	Day 3 (-1 day)	Day 5 (± 1 day)	Day 8 (± 1 day)	Cycles 2-17 Day 1 (± 3 days)	Day 4 (± 1 day) (call or visit)	Notes
Safety Assessments							
Targeted Physical Exam	X				X		Prior to dosing
Vital Signs and Weight	X				X		• Predose (bempegaldesleukin); includes blood pressure, pulse, respiratory rate, temperature, and weight (see Section 8.18) • Within 30 minutes after the end of nivolumab infusion; includes blood pressure, pulse, respiratory rate, and temperature (see Section 8.18)
Local Laboratory Tests	X				X		Within 24 hours (or as soon as locally feasible) prior to dosing to inform dosing decision; see Appendix 1
Local Pregnancy Test	X				X		Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) is required within 24 hours prior to dosing in WOCBP to inform dosing decision; see Section 8.13.1
Central Laboratory Tests	X				X		Within 5 days prior to dosing; see Appendix 1
Performance Status	X				X		See Appendix 3
Adverse Events	Continuous assessment						Record at each visit
Concomitant Medications and Procedures	Continuous assessment						Record at each visit

Procedure[a]	Arm A Bempegaldesleukin (NKTR-214) and Nivolumab Cycle = 3 Weeks (21 days) Cycle 1 Day 1 (≤ 5 days post-randomization)	Cycle 1 Day 3 (-1 day)	Cycle 1 Day 5 (± 1 day)	Cycle 1 Day 8 (± 1 day)	Cycles 2-17 Day 1 (± 3 days)	Cycles 2-17 Day 4 (± 1 day) (call or visit)	Notes
Pharmacokinetic and Exploratory Biomarker Samples							
PK and Immunogenicity Blood Samples	See Section 5.7 and Table 10 for details						
Biomarker Samples	See Section 5.8 [redacted]						
CVA Biomarker Samples	See Section 5.8.2.4 for details						
Outcomes Research Assessments							
EORTC QLQ-C30	X				X		Predose (may be administered by telephone); performed for those ≥ 18 years of age at the time of informed consent, before any other study related procedures, and before the EQ-5D-5L; see Section 5.9 for additional details
EQ-5D-5L	X				X		Predose (may be administered by telephone); performed for those ≥ 18 years of age at the time of informed consent, before any other study-related procedures, and after the EORTC QLQ-C30; see Section 5.9 for additional details

Procedure[a]	Arm A Bempegaldesleukin (NKTR-214) and Nivolumab Cycle = 3 Weeks (21 days) Cycle 1 Day 1 (≤ 5 days post-randomization)	Cycle 1 Day 3 (-1 day)	Cycle 1 Day 5 (± 1 day)	Cycle 1 Day 8 (± 1 day)	Cycles 2-17 Day 1 (± 3 days)	Cycles 2-17 Day 4 (± 1 day) (call or visit)	Notes
Efficacy Assessments							
Imaging Assessment	Every 12 weeks (± 7 days) for up to 24 months from the date of randomization and then every 6 months (± 4 weeks) for up to 5 years (60 months) from the date of randomization; see Section 7.3 for additional details: • CT (contrast-enhanced preferred, unless contraindicated) of chest and CT or MRI (contrast-enhanced preferred, unless contraindicated) of abdomen, pelvis, and all other known sites of resected disease • Ultrasound of sentinel-node basin • Brain imaging for patients with baseline history of treated brain lesions: Brain MRI (without and with contrast; head CT with contrast allowed if patient develops contraindication for MRI) on the same schedule as other imaging • Brain imaging for patients without baseline history of brain metastases: Brain MRI (without and with contrast; head CT with contrast allowed if MRI contraindicated) annually from the date of randomization and as clinically indicated Notes: - Imaging assessment schedule is relative to the date of randomization and will be maintained regardless of dose delays or study drug discontinuation. - Use same imaging method as was used at Screening/Baseline - Continue imaging assessments until investigator-assessed and BICR-confirmed distant recurrence as defined in Section 7.1.						

BICR = blinded independent central review; CRF = case report form; CT = computed tomography; CVA = cerebrovascular accident; EORTC QLQ-C30 = 30-item European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EQ-5D-5L = European Quality of Life – 5 Dimensions Health State Classifier to 5 Levels; HCG = human chorionic gonadotropin; IV = intravenous; MRI = magnetic resonance imaging; PK = pharmacokinetic; WOCBP = women of childbearing potential.

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

Note: If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation.

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

Procedure[a]	Arm B Nivolumab Cycle = 4 Weeks (28 days)			Notes
	Cycle 1		Cycles 2-13	
	Day 1 (≤ 5 days post-randomization)	Day 8 (± 1 day)	Day 1 (± 3 days)	
Study Drug				
Study Drug Administration	X		X	Dispense and administer study drugs following all predose assessments. Following first dose, subsequent doses of study drug may be administered no less than 25 days after prior dose of study drug. If needed, flush the IV line with an appropriate amount of diluent after the nivolumab infusion. Refer to Section 5.3.2 and Pharmacy Manual for details.
Safety Assessments				
Targeted Physical Exam	X		X	Prior to dosing
Vital Signs and Weight	X		X	• Predose; includes blood pressure, pulse, respiratory rate, temperature, and weight (see Section 8.18) • Within 30 minutes after the end of nivolumab infusion; includes blood pressure, pulse, respiratory rate, and temperature (see Section 8.18)
Local Laboratory Tests	X		X	Within 24 hours (or as soon as locally feasible) prior to dosing to inform dosing decision; see Appendix 1
Local Pregnancy Test	X		X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) is required within 24 hours prior to dosing in WOCBP to inform dosing decision; see Section 8.13.1
Central Laboratory Tests	X		X	Within 5 days prior to dosing; see Appendix 1
Performance Status	X		X	See Appendix 3

Procedure[a]	Arm B Nivolumab Cycle = 4 Weeks (28 days)			Notes
	Cycle 1		Cycles 2-13	
	Day 1 (≤ 5 days post-randomization)	Day 8 (± 1 day)	Day 1 (± 3 days)	
Adverse Events	Continuous assessment			Record at each visit
Concomitant Medications and Procedures	Continuous assessment			Record at each visit
Pharmacokinetic [redacted] Biomarker Samples				
PK and Immunogenicity Blood Samples	See Section 5.7 and Table 10 for details			
Biomarker Samples	See Section 5.8 and Table 11 for details			
CVA biomarker samples	See Section 5.8.2.4 for details			
Outcomes Research Assessments				
EORTC QLQ-C30	X		X	Predose (may be administered by telephone); performed for those ≥ 18 years of age at the time of informed consent, before any other study related procedures, and before the EQ-5D-5L; see Section 5.9 for additional details
EQ-5D-5L	X		X	Predose (may be administered by telephone); performed for those ≥ 18 years of age at the time of informed consent, before any other study-related procedures, and after the EORTC QLQ-C30; see Section 5.9 for additional details

Procedure[a]	Arm B Nivolumab Cycle = 4 Weeks (28 days) Cycle 1 Day 1 (≤ 5 days post-randomization)	Cycle 1 Day 8 (± 1 day)	Cycles 2-13 Day 1 (± 3 days)	Notes
Efficacy Assessments				
Imaging Assessment	Every 12 weeks (± 7 days) for up to 24 months from the date of randomization and then every 6 months (± 4 weeks) for up to 5 years (60 months) from the date of randomization; see Section 7.3 for additional details: • CT (contrast-enhanced preferred, unless contraindicated) of chest and CT or MRI (contrast-enhanced preferred, unless contraindicated) of abdomen, pelvis, and all other known sites of resected disease • Ultrasound of sentinel-node basin • Brain imaging for patients with baseline history of treated brain lesions: Brain MRI (without and with contrast; head CT with contrast allowed if patient develops contraindication for MRI) on the same schedule as other imaging • Brain imaging for patients without baseline history of brain metastases: Brain MRI (without and with contrast; head CT with contrast allowed if MRI contraindicated) annually from the date of randomization and as clinically indicated Notes: - Imaging assessment schedule is relative to the date of randomization and will be maintained regardless of dose delays or study drug discontinuation. - Use same imaging method as was used at Screening/Baseline - Continue imaging assessments until investigator-assessed and BICR-confirmed distant recurrence as defined in Section 7.1.			

BICR = blinded independent central review; CRF = case report form; CT = computed tomography; CVA = cerebrovascular accident; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 Questionnaire; EQ-5D-5L = European Quality of Life – 5 Dimensions Health State Classifier to 5 Levels; HCG = human chorionic gonadotropin; IV = intravenous; MRI = magnetic resonance imaging; PK = pharmacokinetic; WOCBP = women of childbearing potential.

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

Note: If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation.

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

Procedure[a]	Safety Follow-up Visit 1[b]	Safety Follow-up Visit 2[b]	Survival Follow-up[c] Every 12 Weeks (± 14 days)	Notes[d]
Safety Assessments				
Vital Signs and Weight	X	X		Blood pressure, heart rate, respiratory rate, temperature
Adverse Event and SAE Assessments	X	X	X	All AEs will be documented until 100 (± 7) days after the last dose of all study treatment(s). Please refer to Section 8.5 and Section 8.8 for details on duration of follow-up for AEs and SAEs.
Performance Status	X	X		See Appendix 3
Review of Subsequent Medications and Anticancer Therapy	X	X	X	In Survival Follow-up, only details regarding subsequent cancer therapy will be collected (see Section 5.5.2). See Section 5.13 for details regarding Safety Follow-up Visits 1 and 2.
Laboratory Tests				
Pregnancy Test	X	X		Patients (WOCBP) will continue to follow instructions for methods of contraception through 5 months after the end of study treatment. For male patients with female partner(s) of childbearing potential, contraception requirements continue until 3 months after the end of bempegaldesleukin treatment (see Appendix 4 for details).
Clinical Laboratory Testing	X	See Notes		During Safety Follow-up Visit 2 if toxicities are present. Refer to Appendix 1 for list of laboratory tests.
Pharmacokinetic and Biomarker Assessments				
PK and Immunogenicity Blood Samples	See Section 5.7 and Table 10 for further details.			
CVA Biomarker Blood Samples	See Section 5.8 and Table 11 for further details.			

Procedure[a]	Safety Follow-up Visit 1[b]	Safety Follow-up Visit 2[b]	Survival Follow-up[c] Every 12 Weeks (± 14 days)	Notes[d]
Efficacy Assessments				
Imaging Assessments	Every 12 weeks (± 7 days) for up to 24 months from the date of randomization and then every 6 months (± 4 weeks) for up to 5 years (60 months) from the date of randomization; see Section 7.3 for additional details: • CT (contrast-enhanced preferred, unless contraindicated) of chest and CT or MRI (contrast-enhanced preferred, unless contraindicated) of abdomen, pelvis, and all other known sites of resected disease • Ultrasound of sentinel-node basin • Brain imaging for patients with baseline history of brain metastases: Brain MRI (without and with contrast; head CT with contrast allowed if patient develops contraindication for MRI) on the same schedule as other imaging • Brain imaging for patients without baseline history of brain metastases: Brain MRI (without and with contrast; head CT with contrast allowed if MRI contraindicated) annually from the date of randomization and as clinically indicated Notes: - Imaging assessment schedule is relative to the date of randomization and will be maintained regardless of dose delays or study drug discontinuation. - Use same imaging method as was used at Screening/Baseline - Continue imaging assessments until investigator-assessed and BICR-confirmed distant recurrence as defined in Section 7.1.			
Survival Status			X	Survival Follow-up can be conducted by telephone; see Section 5.5.2 for additional details
Health Outcomes Assessments				
EORTC QLQ-C30	X	X	X	May be administered by telephone, unless the patient visits the site in which case the paper version can be used; performed before any other study-related procedures and before the EQ-5D-5L;see Section 5.5 and Section 5.9 for additional details
EQ-5D-5L	X	X	X	May be administered by telephone, unless the patient visits the site in which case the paper version can be used; performed before any other study-related procedures and after the EORTC QLQ-C30; see Section 5.5 and Section 5.9 for additional details

AE = adverse event; BICR = blinded independent central review; CRF = case report form; CT = computed tomography; CVA = cerebrovascular accident; eCRF = electronic case report form; EORTC QLQ-C30 = 30-item European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EQ-5D-5L = European Quality of Life – 5 Dimensions Health State Classifier to 5 Levels; MRI = magnetic resonance imaging; PK = pharmacokinetic; SAE = serious adverse event; WOCBP = women of childbearing potential.

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

b. Patients must be followed for 100 (± 7) days after the last dose of study treatment. Safety Follow-up Visit 1 should occur 30 (± 7) days after the last dose of all study treatment(s), or at the time the decision is made to discontinue treatment if discontinuation is after the Safety Follow-up Visit 1 window or before a new antineoplastic regimen starts. Safety Follow-up Visit 2 occurs 100 (± 7) days after the last dose of all study treatment(s). Safety Follow-up Visits should occur regardless of initiation of subsequent anticancer therapy. Both Safety Follow-up Visits should be conducted in person.

c. Survival Follow-up to occur every 12 weeks (± 14 days) following the Safety Follow-up Visit 2 (or 100 [± 7] days after last dose of study treatment). Survival Follow-up may be conducted in person or by telephone. Imaging assessments continue during Survival Follow-up as indicated under Efficacy Assessments. The Sponsor may request that survival data be collected on all treated/randomized patients outside of the 12-week specified window. At the time of this request, each patient will be contacted to determine their survival status unless the patient has withdrawn consent for all contacts or is lost to follow-up. Information about subsequent cancer therapy will also be collected during these contacts.

d. Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used for safety monitoring purposes by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Note: Long-Term Follow-up will continue until the patient withdraws consent, dies or is lost to follow-up, or the study is terminated by the Sponsor (see Section 5.5).

If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation.

2.0 INTRODUCTION

2.1 Background

2.1.1 Melanoma Statistics

Melanoma is the most serious form of skin cancer and affects adults of all ages. Over the last four decades, the incidence of melanoma has increased throughout the world (Siegel, 2019). The World Health Organization's International Agency for Research on Cancer Global Cancer Observatory (GLOBOCAN) estimated that there were nearly 300,000 new cases worldwide in 2018, with most occurring in the World Health Organization European Region (144,209; 50%) and North America (79,644; 28%). Of > 60,000 deaths from melanoma in 2018, most also occurred in Europe (27,147; 45%) and North America (10,733; 18%) (Ferlay, 2018). In the United States (US), it is estimated that there will be 100,350 new cases of melanoma and 6,850 deaths from the disease in 2020 (American Cancer Society, 2020). The vast majority of patients (approximately 84%) diagnosed with cutaneous melanoma in the US present with clinically localized disease, while 9% of patients have regional disease at presentation and 4% have distant metastasis (Siegel, 2018).

According to the data from the Eighth Edition International Melanoma Database, 5-year melanoma-specific survival is 98%, 90%, and 77% for Stage I, II, III melanoma, respectively, and as low as 32% for the Stage IIID melanoma subgroup (Gershenwald, 2017). The 5-year survival rate for Stage IV melanoma has been 25% (American Cancer Society, 2020) but is continuing to evolve with the approval of a number of treatment options including immunotherapy and targeted therapy that improve survival. In a study of adult patients with previously untreated, unresectable or metastatic Stage III or IV melanoma, the 5-year overall survival (OS) was higher in those treated with nivolumab plus ipilimumab (52%) and nivolumab alone (44%) than those treated with ipilimumab alone (26%) (Larkin, 2019).

Resected localized and regionally advanced melanomas with lymph node involvement are at high risk of recurrence, and in turn, recurrence is associated with poor survival outcomes. In large global adjuvant studies of patients with resected melanoma, the 5-year recurrence-free survival (RFS) rates among patients with resected Stage III disease were as low as 30% among patients treated with placebo and 41% among patients treated with ipilimumab (Eggermont, 2016), and the 1-year RFS rates were 62% among patients treated with ipilimumab and 72% among patients treated with nivolumab (Weber, 2017). A large retrospective observational study assessing stage-specific disease recurrence and survival in patients with resected Stage I, II or III cutaneous melanoma showed that recurrence impacted survival, regardless of stage, with post-recurrence OS of 1.9 years, 1.5 years, and 1.1 years for patients with Stage I, II and III disease, respectively (Leeneman, 2019). Therefore, improvements in adjuvant therapy have the potential to reduce or further delay recurrence and extend survival in patients with resected melanoma.

2.1.2 Nivolumab

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

2.1.2.1 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death (Foley, 1953). Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses (Pardoll, 2003; Zitvogel, 2006; Dunn, 2002). Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. CD8+ T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the CD8+ T-cell receptor (Greenwald, 2004). Collectively, these signals govern the balance between CD8+ T-cell activation and tolerance.

Programmed cell death protein 1 (PD-1) is a member of the CD28 family of CD8+T-cell co-stimulatory receptors that also includes CD28, CTLA-4 (cytotoxic T lymphocyte-associated protein 4), inducible T-cell co-stimulator, and BTLA (Freeman, 2000). PD-1 signaling has been shown to inhibit CD28-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 CD8+ T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (50% effective dose [EC_{50}] 0.39 to 2.62 nM), and inhibits the binding of PD-1 to its ligands programmed cell death ligand 1 (PD-L1) and PD-L2 (50% inhibitory dose [IC_{50}] ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, inducible T-cell co-stimulator, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus restimulation assay with human peripheral blood mononuclear cells (PBMCs), the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-γ secretion from cytomegalovirus-specific memory T cells in a dose-

dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) (Wolchok, 2009).

2.1.2.2 Nivolumab for Adjuvant Treatment of Melanoma

The CheckMate 238 study (CA209238) evaluated adjuvant nivolumab versus ipilimumab in patients with resected stage IIIB/C or Stage IV melanoma. At a median of 19.5 months of follow-up, nivolumab was associated with a clinically meaningful and statistically significant improvement in RFS and distant metastasis-free survival (DMFS). The percent of patients experiencing Grade 3 to 4 adverse events (AEs) was 30% lower in the nivolumab versus ipilimumab arm (Weber, 2017). Subgroup analyses suggest that nivolumab significantly improves RFS (relative to ipilimumab) regardless of BRAF mutation status or PD-L1 expression status (using the 28-8 antibody at 5% cutoff for PD-L1 staining). The demonstrated improvement in RFS led to the US Food and Drug Administration (FDA) approving nivolumab for adjuvant treatment of resected nodal or metastatic melanoma. It is notable that while the trial enrolled patients with Stage IIIB/C disease (American Joint Committee on Cancer [AJCC] 7th edition) who had clinically detected lymph nodes and/or ulcerated primary lesions, the FDA-approved indication for nivolumab is broader and includes all patients with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting. Nivolumab is also approved by the European Medicines Agency for adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

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 6 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 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, 2016; Charych, 2017; Bentebibel, 2019; Parisi, 2020; Sharma, 2020). Consistent with this mechanism of action, recent nonclinical studies demonstrate strong synergy of bempegaldesleukin with adoptive T cell therapy, 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, 2020a).

The immunological properties of bempegaldesleukin with the induction of tumor-infiltrating lymphocytes 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 complementary 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 (q3w) was deemed the MTD by predefined 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 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, 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 IL-2 mediated AEs generally occurred 3 to 4 days after dosing and corresponded to the time of peak plasma concentration of the active cytokines. The flu-like symptoms were managed with acetaminophen and nonsteroidal anti-inflammatory drugs 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 IV fluids, and a hydration management guideline was implemented during the study which mitigated the hypotension severity. One patient, who had a prior history of an infusion reaction to a previously administered immunotherapy, discontinued treatment due to an infusion-related reaction following the first dose of bempegaldesleukin 0.009 mg/kg. With the exception of one event of hypothyroidism, no other immune-mediated AEs consistent with checkpoint inhibitors were reported. No patient experienced capillary leak syndrome and no Grade 4 treatment-related AEs or treatment-related deaths were reported on the study.

Fifteen patients (53.6%) reported 31 serious adverse events (SAEs) in monotherapy Study 15-214-01. Eleven SAEs reported among 7 (25.0%) patients were considered related to treatment. The only treatment-related SAE reported for > 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 (SD) in 14 patients (50%), progressive disease in 12 patients (42.9%), and not evaluable (NE) for 2 patients (7.1%). While no objective responses were observed in Study 15-214-01, 9 patients experienced tumor shrinkage between 1% and 30% and 2 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 (i.e., 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 to 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 objective response rate (ORR) at the RP2D. The indications studied in Part 2 include melanoma, RCC, non-small cell lung cancer (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 + nivolumab dose escalation portion of PIVOT-02 has been completed, with the safety results of bempegaldesleukin at 0.006 mg/kg in combination with nivolumab 360 mg q3w indicating no dose-limiting toxicities and no Grade ≥ 3 treatment-related AEs at the time of completion. Bempegaldesleukin 0.006 mg/kg in combination with nivolumab 360 mg q3w was the recommended dose regimen to be taken forward into expansion cohorts in Part 2.

As of 28 October 2020, a total of 557 patients had been treated with bempegaldesleukin in combination with nivolumab (503 patients with doublet [bempegaldesleukin and nivolumab]; 43 patients with triplet [bempegaldesleukin, nivolumab, and ipilimumab]; and 11 patients with doublet [bempegaldesleukin and nivolumab] plus other anticancer study drug). Of the 557 patients, most have NSCLC (184 patients [33%]), RCC (139 [25%]), or melanoma (102 [18%]), followed by urothelial carcinoma (61 [11%]), breast cancer (47 [8%]), CRC (22 [4%]), and gastric cancer (2 [< 1%]). The median duration of exposure was 106.0 days (doublet, 101.0; triplet, 179.0; doublet plus other anticancer drug, 113.0) (range: 1 to 817 days).

As of 28 October 2020, among the 503 patients who received the doublet:

- 94.6% (476 of 503) of patients reported treatment-related AEs; the most frequent were fatigue (47.1%), pyrexia (44.7%), pruritus (36.0%), nausea (31.4%), influenza-like illness (26.8%), decreased appetite (26.6%), rash (26.0%), and chills (25.8%).
- 24.9% (125 of 503) of patients reported treatment-related, Grade ≥ 3 AEs; the most frequent were syncope (2.8%), hypotension (2.6%), and lipase increased (2.2%).
- 16.3% (82 of 503) of patients reported treatment-related SAEs; the most frequent were pyrexia (3.0%), 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, 25 were treated at 0.006 mg/kg bempegaldesleukin combined with nivolumab 360 mg flat dose every 3 weeks. As of 18 January 2019, 22 of 37 response-evaluable patients (59.5%) achieved an investigator-assessed response (complete or partial response) by RECIST 1.1 (Diab, 2020a).

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) ORR via blinded independent central review (BICR) was observed (N = 41 enrolled; N = 38 included in the N1 + N2 population; Diab, 2020b; 01 Sep 2020 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 July 2019 data cutoff).

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

2.1.3.2.3 Clinical Experience of Bempegaldesleukin in Combination with Nivolumab in Melanoma

The 1L melanoma cohort (n = 41; 38 response evaluable) of Study 16-214-02 (PIVOT-02) has demonstrated clinical evidence that bempegaldesleukin plus nivolumab provides substantial and highly clinically relevant improvement in CR rates compared with available therapies (Hurwitz, 2019). With data cutoff of 29 March 2019, and with a median follow-up of 12.7 months, the confirmed ORR by independent central radiology was 52.6% (20/38) (95% confidence interval [CI] 35.8%, 69.0%) for bempegaldesleukin plus nivolumab, with a CR rate of 34.2% (13/38) (95% CI 19.6%, 51.4%). The combination of bempegaldesleukin plus nivolumab was granted Breakthrough Therapy Designation in July 2019 by the FDA. The clinical efficacy appeared to be durable. With a data cutoff of 25 September 2019, and with a median follow-up of 18.6 months, 41 patients with 1L locally advanced and metastatic melanoma received bempegaldesleukin plus nivolumab at the RP2D; 38 of these patients with measurable disease (per RECIST 1.1) at baseline had at least one post-baseline tumor assessment

and were included in the response evaluable population; the other 3 patients discontinued prior to first scan due to an unrelated treatment-emergent AE (n=1) or patient decision (n=2). The ORR was 52.6% (20/38; 95% CI 35.8%, 69.0%). Notably, however, 13 of 20 responders (65%) achieved confirmed CR, with a CR rate of 34.2% (13/38; 95% CI 19.6%, 51.4%) in the response evaluable population; partial response rate was 18.4% (7/38). For the intent-to-treat (ITT) population, CR rate was 31.7% (13/41). The median time to response was 2.0 months and deepening of response over time was observed; median time to CR was 7.9 months. Duration of response ranged from 4.2 months to at least 26.1 months; median duration of response has not yet been reached as the majority of responders (17 of 20 [85.0%]) still had ongoing responses at data cutoff. The median progression-free survival was not yet reached. Responses from bempegaldesleukin plus nivolumab are deep and durable: the median tumor reduction from baseline was 61.5%, and 80% of patients with responses had 100% reduction in target lesions, and 80% of patients had ongoing responses at the time of data cutoff. Furthermore, responses were observed across various prognostic subgroups and biomarker subsets. Responses to treatment with bempegaldesleukin plus nivolumab were seen regardless of PD-L1 status (PD-L1 positive; PD-L1 negative), BRAF status (mutation; no mutation), presence of liver metastases (yes; no), lactate dehydrogenase (LDH) levels (high; normal), and metastatic stage (M1a. M1b, M1c).

Historically, nivolumab alone has demonstrated an ORR of 40% (95% CI 33.3%, 47.0%) with CR rate of 7.6% (Robert, 2015). Nivolumab plus ipilimumab was approved with an ORR of 50% and CR rate of 8.9% (Opdivo PI, 2021). Combination of targeted therapies, such as dabrafenib plus trametinib, may have higher response rates, but the CR rate is lower than that observed with bempegaldesleukin plus nivolumab (for example, dabrafenib plus trametinib, ORR 64%, CR 13% at 12 months of follow-up) (Flaherty, 2012).

The safety profile from the 1L melanoma cohort (n = 41) of Study 16-214-02 (PIVOT-02) with data cutoff of 29 March 2019 was consistent with the overall safety profile from all patients treated with bempegaldesleukin plus nivolumab described in the Investigators Brochure (N = 358). No new safety signals were identified, no fatal AEs were reported from the melanoma cohort and the reported AEs were reversible and manageable with established management guidelines. The frequencies of Grade ≥ 3 AEs and AEs leading to discontinuation of treatment (in 19 [46.3%] and 7 [17.1%] patients, respectively) were similar to those in nivolumab monotherapy, and ~1.6- to 3-fold lower than those in nivolumab plus ipilimumab (Schadendorf 2016; Opdivo PI, 2021). In addition, although cases that are consistent with immune-mediated AEs associated with checkpoint inhibitors, such as pneumonitis, hepatitis, and endocrinopathy have been observed in patients treated with bempegaldesleukin plus nivolumab, there is no evidence suggesting increased frequency or severity over nivolumab alone.

Clinical data from the 1L melanoma cohort of PIVOT-02 led to bempegaldesleukin plus nivolumab receiving Breakthrough Therapy Designation on 29 July 2019 from the FDA for patients with previously untreated, unresectable or metastatic melanoma.

The CA045-001 (PIVOT-IO-001) study is a global, Phase III, randomized, open-label study of bempegaldesleukin plus nivolumab versus nivolumab monotherapy in patients with previously untreated, unresectable or metastatic melanoma. This study started enrollment in September 2018 and is currently enrolling with a planned sample size of 764 patients.

2.1.3.2.4 Pooled Safety Analysis of Patients with Bempegaldesleukin and Nivolumab Exposure

A pooled safety analysis (28 October 2020 data cutoff) is available of patients who received the bempegaldesleukin and nivolumab doublet from the ongoing combination Phase 1/2 studies (16-214-02 and 16-214-05), the ongoing combination Phase 2 study (18-214-10), and the completed Phase 1 study (CA045-010). Of the 696 patients who received the bempegaldesleukin and nivolumab doublet:

- 93.0% (647 of 696) of patients reported treatment-related AEs; the most frequent were pyrexia (42.1%), fatigue (39.9%), pruritis (37.6%), nausea (27.9%), rash (24.6%), decreased appetite (23.7%), influenza-like illness (22.4%), and chills (22.1%).
- 24.6% (171 of 696) of patients reported treatment-related, Grade ≥ 3 AEs; the most frequent were hypotension (2.6%), fatigue (2.0%), arthralgia (1.1%), pyrexia (1.1%), and diarrhea (0.9%).
- 15.8% (110 of 696) of patients reported treatment-related SAEs; the most frequent were pyrexia (2.6%), hypotension (1.7%), dehydration (0.9%), pneumonitis (0.7%), acute kidney injury, atrial fibrillation, and myocarditis (0.6% each).

2.1.3.2.5 Observed Events of Cerebrovascular Accident

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

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 (PIVOT-02) were reported to have CVA events, including one fatal event, all of which 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 combined 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.

2.1.3.2.5.2 Updated Analysis of CVA Events Observed with Bempegaldesleukin

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

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

Based on these events, CVA was escalated to an adverse event of special interest (AESI) and mitigations were put in place to reduce the risk of CVA. These mitigations include implementation of a CVA adverse event management algorithm (Appendix 6) and updates to the exclusion criteria, renal function and hydration assessment, hydration guidelines, concomitant and prohibited medications, dose modification guidelines, and discontinuation criteria. Additional information on the clinical safety and risk of CVA is found in the bempegaldesleukin Investigator's Brochure.

2.2 Scientific Rationale for Study Design

2.2.1 Standard of Care for Melanoma

Treatment for melanoma involves removal of the primary tumor and surrounding normal tissue and sentinel lymph node biopsy to determine stage. Subsequent more extensive lymph node surgery may be necessary if lymph node metastases are present. However, the value of completion lymph node dissection remains controversial. In the Multicenter Selective Lymphadenectomy Trial (MSLT-II), immediate completion lymph node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival compared to nodal observation with ultrasonography and was associated with higher morbidity (Faries, 2017). Based on these results, completion lymph-node dissection is no longer a routine standard of care for patients with resected node-positive disease, and regular ultrasound surveillance of the nodal basin is preferred.

Even with complete resection, surgery alone is not sufficient to achieve cure for patients with advanced melanoma. Adjuvant treatment with systemic therapy after surgical resection has attempted to improve survival for patients with higher risk of recurrence over the last two decades. Adjuvant high-dose interferon alpha has been used for many years, but recent meta-analyses including data from a large number of trials have shown only modest

improvements in RFS and OS (Ives, 2017). Over the last several years, multiple new systemic therapies have shown improvements in RFS in the adjuvant treatment for high risk, resected melanoma. Results from these trials are summarized in Table 5.

Table 5: Immune Checkpoint Inhibitor and Targeted Therapy for Adjuvant Treatment of Melanoma: Pivotal Studies

Trial	Stages Included (AJCC 7th Ed)	Treatment Arms	Median Follow-up	RFS or DFS	DMFS	OS
Immune Checkpoint Inhibitors						
EORTC 18071 Eggermont, 2016	IIIA>1mm IIIB/C	Ipilimumab (n=475) Placebo (n=476)	5 years	5-year: 41% vs 30% HR = 0.76	5-year: 48% vs 39% HR = 0.76	5-year: 65% vs 54% HR = 0.72
Eggermont, 2019			7 years	7-year: 39% vs 31% HR = 0.75	7-year: 45% vs 37% HR = 0.76	7-year: 60% vs 51% HR = 0.73
CheckMate 238 Weber, 2017	IIIB/C IV	Nivolumab (n=453) Ipilimumab (n=453)	1.5 years	1-year: 71% vs 61% HR = 0.65	1-year: 25% vs 31% HR = 0.73	NR
Weber, 2019			36 months	3-year: 58% vs 45% HR = 0.68	3-year: NR HR = 0.78	NR
Ascierto, 2020			4 years	4-year: 52% vs 41% HR = 0.71	4-year: NR HR = 0.79	4-year: 78% vs 77% HR = 0.87
KEYNOTE-054 Keytruda Assessment Report, 2018	IIIA>1mm IIIB/C	Pembrolizumab (n=514) Placebo (n=505)	21.6 months	12 months: 76% vs 61% 18 months: 72% vs 54% 24 months: 67% vs 49% HR = 0.56	NR	NR
Eggermont, 2020			3.05 years	3-years: 64% vs 44% HR = 0.56	NR	NR

Table 5: Immune Checkpoint Inhibitor and Targeted Therapy for Adjuvant Treatment of Melanoma: Pivotal Studies (Cont'd)

Trial	Stages Included (AJCC 7th Ed)	Treatment Arms	Median Follow-up	RFS or DFS	DMFS	OS
BRAF-Targeted Therapy						
COMBI-AD Long, 2017	IIIA>1mm IIIB/C	Dabrafenib + Trametinib (n=438)	2.8 years	3-year: 58% vs 39% HR = 0.47	3-year: NR HR = 0.51	3-year: 86% vs 77% HR = 0.57
Hauschild, 2018		Placebo (n=432)	Treatment: 44 months Placebo: 42 months	4-year: 54% vs 38% HR = 0.49	4-year: 67% vs 56% HR = 0.53	NR
Hauschild, 2020			Treatment: 60 months Placebo: 59 months	5-year: 52% vs 36% HR = 0.51	NR HR = 0.55	NR

AJCC = American Joint Committee on Cancer; DFS = disease-free survival; DMFS = distant metastasis-free survival; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; NR = not reached; OS = overall survival; RFS = recurrence-free survival.

Further improvement in the outcome for patients with completely resected melanoma is needed.

Note that all of the trials in Table 5 used AJCC 7th edition staging, whereas the AJCC 8th edition has been adopted since the beginning of 2018. Each trial in Table 5 included a subset of Stage III disease deemed sufficiently high risk to warrant adjuvant treatment, but the definitions of "high risk" differed. Currently approved adjuvant immunotherapies in the US and European Union for Stage III melanoma with lymph node involvement and Stage IV disease (for nivolumab only) after complete surgical resection include ipilimumab (US only), nivolumab, and pembrolizumab. Dabrafenib plus trametinib is approved for completely resected Stage III melanoma with BRAF V600E or V600K mutations and involvement of lymph nodes.

2.2.2 Rationale for the Combination of Bempegaldesleukin and Nivolumab

See Section 2.1.3.2.3.

2.2.3 Rationale for Nivolumab

See Section 2.1.2.2.

2.2.4 Rationale for Patient Population

Revisions to AJCC staging have been made to be concurrent with advances in surgical care and systemic therapy and further improve prognostication to inform increasingly complex therapeutic decision making. The AJCC 7th edition was derived from data that included patients from the 1960s, well before sentinel lymph node biopsy provided accurate staging of the regional lymph

node basin. The AJCC 8th edition, which was adopted early in 2018, included only melanoma patients from 1998 onwards, those with sentinel lymph node staging and follow-up. Furthermore, the International Melanoma Database and Discovery Platform consists of data from over 40,000 melanoma patients across 14 institutions in Australia, Europe, and the US who have complete staging information. Definition for "high risk" in this study is based on melanoma-specific survival data as prognostic factor in the database according to AJCC 8th edition. Nivolumab is approved (ex-US) for the adjuvant treatment of patients (adults) with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. In Stage III (AJCC 8th edition), patients with Stage IIIB/C and the new Stage IIID are at high risk for recurrence.

Table 6: Prognosis Implications of the AJCC 8th Edition on Melanoma Staging

Stage III					
Stage	**T**	**N**	**5-year MSS, %**	**10-year MSS, %**	**n**
IIIA	≤ T2a	≤ N2a	93	88	1066
IIIB	≤ T2a	≤ N2b	**83**	77	1170
IIIC	≤ T3a T3b/T4a T4b	N2c or N3 ≥ N1 N1a to N2c	**69**	**60**	2201
IIID	T4b	N3	**32**	**24**	205

AJCC = American Joint Committee on Cancer; MSS = melanoma-specific survival; n = number of patients in the International Melanoma Database used for stage designation.

Source: Crompton, 2019

Of note, although Stage IIIA patients overall appear to have favorable melanoma-specific survival (Table 6), it has been acknowledged that patients with lymph node metastasis > 1 mm have significantly worse prognosis than those with less lymph node involvement (van Akkooi, 2008; van der Ploeg, 2011; van der Ploeg, 2014; Gershenwald, 2017). Therefore, patients with Stage IIIA melanoma with lymph node metastasis > 1 mm are also considered to be at higher risk of recurrence.

Lastly, consistent with CheckMate 238, patients with Stage IV melanoma that have been completely surgically resected are also considered at high risk of recurrence.

In summary, since adjuvant systemic therapy is appropriate for patients at high risk for recurrence, the patient population appropriate for this trial are those with Stage IIIA (with lymph node [LN] metastasis > 1 mm), IIIB/C/D, and IV melanoma (AJCC 8th edition) that have been completely surgically resected.

2.2.5 Rationale for Inclusion of Adolescent Patients

Adolescent (generally aged 12 to 17 years) enrollment into clinical trials has been historically lower than enrollment of their pediatric counterparts. Lack of participation in pediatric trials may be due to differences in tumors observed in adolescent patients versus their pediatric counterparts, as tumors in adolescents may mirror those observed more often in adults. In addition, once a drug is approved for use in adults, enrollment of adolescent patients in pediatric studies may also be difficult because patients can receive the drug through off-label use. For trials in adult patients with tumor types that also occur in adolescents, adolescents are often excluded due to safety or regulatory concerns. Overall, this has led to a delay in the study of new therapies in adolescents, and most problematically, a delay in new, efficacious therapies reaching this population. It has been recommended, therefore, that adolescents be considered for trials in adult populations for tumor types that are observed in adolescents and that share features common to those tumors that occur in adults (Chuk, 2017; Beaver, 2017).

A recent genomic analysis of pediatric melanoma demonstrated that conventional melanoma in children and adolescents shares many of the genomic features that have been described in adult melanoma, including BRAF mutations (Beaver, 2017). Given the similarities observed in adolescent melanoma compared to adult, as well as the overarching need for inclusion of adolescents in clinical trials of potentially new, efficacious therapies, adolescents will be included in this study where locally permitted. Individual countries and sites have the option of opting out of adolescent eligibility. A Phase 3 clinical study evaluating the efficacy and safety of bempegaldesleukin in combination with nivolumab versus nivolumab (Protocol CA045001/ 18-214-08) in patients ages 12 years or older with treatment-naïve advanced or metastatic melanoma is also ongoing in multiple countries.

2.2.6 Rationale for Primary Endpoint (RFS) and Key Secondary Endpoints (OS and DMFS)

After complete surgical resection, there is no measurable disease to follow and recurrence is detected with surveillance scans, both during the treatment period for adjuvant therapy and afterwards until recurrence is documented. RFS in melanoma is a clinically meaningful endpoint, which is associated with OS and is the primary endpoint for this study. There are a number of marketed treatment regimens in the metastatic setting that are known to improve OS. Although post study treatment may confound the assessment of OS, OS has been the gold standard for demonstrating clinical benefit for cancer drugs and is a key secondary endpoint for this trial.

Although any recurrence (i.e. local, regional, or metastatic) is accounted for in RFS, it is clinically meaningful to determine the time to distant metastasis, which directly impacts OS. In other words, since a local recurrence or a regional recurrence can be treated with curative intent by appropriate surgical intervention and possibly further adjuvant systemic treatment, distant metastasis is incurable and more directly correlates with OS. Therefore, DMFS by Investigator, defined as the time from randomization until first occurrence of distant metastasis or death, is another key secondary endpoint of the study.

2.2.7 Rationale for Stratification Factors

PD-L1 status is one of the key stratification factors in this study and is intended to evaluate whether PD-L1 status is a predictive biomarker for RFS. Furthermore, the revised staging per AJCC 8th edition has shown clear prognostic differences with various stages in melanoma at high risk for recurrence after complete resection (see Section 2.2.4). In this study, stages of disease per AJCC 8th edition are stratified per similar prognostic implications as follows: Stage IIIA (LN metastasis > 1 mm)/IIIB vs IIIC vs IIID/IV.

2.2.8 Rationale for Open-Label Design

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

The trial will have an open-label design with a BICR. There are multiple reasons that would make blinding the trial impractical or impossible: 1) requirement to follow the hydration guidelines for bempegaldesleukin; 2) potential need to hold anti-hypertensive medications for patients on the bempegaldesleukin arm but not on nivolumab monotherapy arm; 3) blinding treatment arms with different dosing schedules between the 2 arms would require multiple placebo infusions and multiple additional visits; 4) the common side effect profile of bempegaldesleukin (e.g., flu-like symptoms) will be unblinding. Therefore, a placebo-controlled, double-blinded design is not appropriate for this study.

2.2.9 Duration of Treatment for Bempegaldesleukin Combined with Nivolumab

The optimal duration of immunotherapy is an important question and continues to be investigated. A treatment duration of up to approximately 1 year is planned for this study to align with the standard duration of the nivolumab monotherapy comparison arm. Patients will be treated until BICR-confirmed disease recurrence or other treatment discontinuation criteria are met (Section 5.12). An exception is that patients with recurrence of malignant melanoma in situ (MMIS) Stage 0 melanoma will be permitted to continue study treatment based on Investigator judgment.

Stage 0 melanomas are not invasive by definition and do not present a risk of developing metastatic disease. The risk of death develops from advanced Stage IIIB/C/D or Stage IV melanoma for which they are receiving treatment during the clinical trial. Consequently, in the absence of intolerable toxicity, patients with diagnosed MMIS Stage 0 melanoma while on treatment will be eligible to continue adjuvant study treatment for up to approximately 1 year of study treatment from the time of randomization, at the discretion of the Investigator.

2.3 Justification for Dose

2.3.1 Justification for Dose of Bempegaldesleukin

The dose for bempegaldesleukin is 0.006 mg/kg q3w taking into consideration the clinical safety profile associated with the robust immune system activation observed in the PIVOT-02 study. Please refer to Section 2.1.3.2.2 for additional details on PIVOT-02.

Justification for Dose in Adolescents

Using physiologically-based pharmacokinetic (PK) modeling to simulate exposure in pediatric patients, the predicted exposure to NKTR-214 in the pediatric population (including adolescents) was found to be similar to adults. The model included PK data following administration of NKTR-214 (0.006 mg/kg) with nivolumab (360 mg) in adults. The model-based NKTR-214 AUC ratio between adolescents (12 to 18 years of age) and adults was 0.94, while the maximum observed concentration (C_{max}) ratio was 0.96. Thus, the body weight adjusted dose of 0.006 mg/kg is expected to provide similar exposure to bempegaldesleukin in adults and adolescents.

2.3.2 Justification for Dose of Nivolumab

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

The benefit-risk profile of nivolumab 360 mg q3w is predicted to be comparable to 3 mg/kg q2w. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and exposure-response relationships across indications. Population pharmacokinetic (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no differences in PK across ethnicities were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including nivolumab 360 mg q3w. The simulated average concentration at steady state following administration of nivolumab 360 mg q3w are expected to be similar to those following administration of nivolumab 240 mg q2w and nivolumab 3 mg/kg q2w administered to patients over a wide body weight range (34 to 180 kg) across tumor types. Given that the average concentration at steady state estimates for nivolumab 360 mg q3w are predicted to be similar to those for nivolumab 240 mg q2w, nivolumab 480 mg q4w, and nivolumab 3 mg/kg q2w, the efficacy is predicted to be similar for these regimens. Additionally, flat exposure-safety and exposure-efficacy response curves in advanced melanoma have been observed from 240 mg q2w to 480 mg q4w (Zhao, 2020).

For the experimental arm, nivolumab 360 mg q3w is used because this is the RP2D identified for the combination with bempegaldesleukin (q3w) in the PIVOT-02 study and is being investigated in multiple studies of this combination, including in metastatic melanoma.

For the control arm, nivolumab 480 mg q4w is chosen because this regimen is globally approved (US and EU) for adjuvant melanoma and reduces burden on patients and sites with fewer visits needed for administration compared to the 240 mg q2w regimen, which is the other dose approved for adjuvant melanoma. Approval of nivolumab 480 mg q4w in adjuvant melanoma was based on comparability of PK and exposure-response data among nivolumab 240 mg q2w, 3 mg/kg q2w, and 480 mg q4w dosing regimens.

Justification for Dose in Adolescents

The PK of drugs and many therapeutics proteins have been shown to be similar between adolescent and adults once the effect of body size on PK is taken into consideration. Therefore, in general, adult doses would be expected to achieve similar systemic exposures in adolescents. PPK model-based simulation has shown that exposures produced by nivolumab 360 mg q3w were well below the exposure range of 10 mg/kg q2w regimen, a clinically safe dose, over a dose range of 34 to 180 kg in adults. Therefore, a minimum body weight threshold in adolescents (≥ 40 kg) is defined to receive the same adult flat dose to prevent exceeding target adult exposures (Xu, 2013; Zhang, 2015).

Patients < 40 kg body weight will be given a weight-based dose that is equivalent to an adult dose (typical subject of 80-kg body weight). Patients ≥ 40 kg will be administered nivolumab 360 mg q3w with bempegaldesleukin or 480 mg q4w monotherapy. Patients < 40 kg will be administered the body weight-adjusted nivolumab dose 4.5 mg/kg q3w or 6.0 mg/kg q4w in the bempegaldesleukin plus nivolumab arm and nivolumab monotherapy arm, respectively.

Additional details on dosing are provided in the nivolumab Investigator's Brochure, Prescribing Information (Opdivo PI, 2021), and Summary of Product Characteristics (Opdivo SmPC, 2020).

2.4 Benefit/Risk Assessment

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

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

2.4.2 Nivolumab Safety Profile

Extensive details on the safety profile of nivolumab are available in the Investigator's Brochure, Prescribing Information (Opdivo PI, 2021), and Summary of Product Characteristics (Opdivo SmPC, 2020) and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in the Investigator's Brochure. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab Investigator's Brochure, Prescribing Information (Opdivo PI, 2021), and Summary of Product Characteristics (Opdivo SmPC, 2020).

2.4.3 Bempegaldesleukin and Nivolumab Benefit and Risk Assessment

Bempegaldesleukin has been generally well-tolerated in the clinical studies to date, both as monotherapy as well as in combination with nivolumab, with promising evidence of clinical efficacy and a potentially favorable benefit-risk profile. 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 IL-2 mediated AEs (e.g., flu-like symptoms, rash, pruritus, fatigue, hepatic transaminase elevations, and serum creatinine elevation), infusion-related reactions, thyroid dysfunction, eosinophilia, and arthralgia; these AEs are generally mild or moderate in severity, and can be monitored and managed in clinical setting. Cases of thyroid dysfunction (hypothyroidism, hyperthyroidism, thyroiditis), dermatitis, pneumonitis, hepatitis, myocarditis, myositis/myasthenia gravis, and vitiligo/hypopigmentation consistent with immune-mediated mechanism have been observed in patients receiving bempegaldesleukin plus nivolumab, and some of these cases shared clinical characteristics consistent with immune-mediated AEs associated with checkpoint inhibitors.

The continued development of bempegaldesleukin in combination with nivolumab for the treatment of various cancers is warranted based on a positive benefit-risk profile. In addition, the

early efficacy data along with the correlative biomarker showing conversion of PD-L1 negative patients to PD-L1 positive patients suggests that the addition of bempegaldesleukin to a checkpoint inhibitor (nivolumab) may change the tumor microenvironment in PD-L1 negative patients such that the combination may contribute to antitumor activity with an acceptable safety profile.

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

2.4.4 Independent Data Monitoring Committee

In addition to routine safety monitoring and pharmacovigilance activities, an Independent Data Monitoring Committee (IDMC) will be formed to independently monitor and assess accumulating safety data and emerging benefit-risk balance at regular intervals throughout the study, at the interim analyses, and on an ad hoc basis as detailed in the IDMC charter (see Section 9.10).

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to compare the efficacy, as measured by RFS by BICR, of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (LN metastasis > 1 mm), Stage IIIB/C/D, or Stage IV (AJCC 8th edition) cutaneous melanoma with no evidence of disease (NED) who are at high risk for recurrence.

3.2 Secondary Objectives

The secondary objectives are:

- To compare the OS of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (LN metastasis > 1 mm), Stage IIIB/C/D, or Stage IV NED melanoma
- To evaluate DMFS by BICR and by Investigator in patients who have Stage IIIA (LN metastasis > 1 mm) or IIIB/C/D melanoma at study entry
- To evaluate time to disease progression after the next line of treatment for study patients following discontinuation of bempegaldesleukin plus nivolumab versus nivolumab
- To assess the overall safety and tolerability of bempegaldesleukin plus nivolumab versus nivolumab in study patients
- To describe changes in patient-reported outcomes (PROs) as assessed by the global health/quality of life (GH/QoL) and physical functioning subscales of the 30-item European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30)
- To evaluate the association between PD-L1 expression status and RFS by BICR
- To assess the efficacy, as measured by RFS by Investigator, of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (LN metastasis > 1 mm), Stage IIIB/C/D, or Stage IV NED melanoma

3.3 [redacted]

[redacted]

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

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

1. Provide written, informed consent to participate in the study and follow the study procedures. The Investigator takes responsibility for ensuring that all vulnerable patients are protected and participate voluntarily in an environment free from coercion or undue influence. (See Section 5.2 for details about obtaining informed consent for adolescent patients.)
2. Male or female patients ≥ 12 years of age at the time of signing the informed consent form (ICF), except where local regulations, countries, and/or institutional policies do not allow for patients < 18 years of age (adolescents) to participate. In regions where adolescents are not allowed to participate in the study due to age restrictions, enrolled patients must be ≥ 18 years of age.
3. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (≥ 17 years of age)/Lansky Performance Score ≥ 80% (12 to 16 years of age, inclusive) (for details, see Appendix 3).
4. Histologically confirmed Stage IIIA (LN metastasis > 1 mm [i.e., at least one LN metastasis measuring > 1 mm at greatest diameter]), IIIB/C/D, or IV (M1a/b/c/d) cutaneous melanoma by AJCC (8th edition) at study entry.
   - Patient must be completely surgically resected within 12 weeks prior to randomization.
   - Patients with in-transit or microsatellite disease will be allowed if disease has been completely surgically resected.
   - Patients must have been surgically rendered free of disease with negative surgical margins documented, as applicable.

   Please refer to Section 5.2 for details of minimum documentation requirements and Appendix 2 for AJCC 8th edition definitions of TNM and staging.
5. Prior treated central nervous system (CNS) metastases must have magnetic resonance imaging (MRI) evidence of no recurrence for at least 4 weeks after treatment, subjects must be off immunosuppressive doses of systemic steroids (> 10 mg/day or equivalent) for at least 14 days prior to study drug administration and must have returned to neurologic baseline post-operatively. (The 4-week period of stability is measured after the completion of the neurologic interventions [i.e., surgery and/or radiation]). (Note: Leptomeningeal disease is excluded.)
6. In addition to neurosurgery to treat CNS metastases, adjuvant radiation after the resection of CNS metastasis is allowed. Immunosuppressive doses of systemic steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 14 days before study drug administration.

7. Tumor tissue available from biopsy or resected disease must be provided to central laboratory for biomarker and PD-L1 status analysis. Must have PD-L1 expression classification (≥ 1%, < 1%, indeterminate, or not evaluable) prior to randomization.
8. Disease-free status documented by a complete physical examination and imaging studies within 28 days prior to randomization (see Table 1 for details of required assessments).
9. Demonstrated adequate organ function, as defined below:
    a. White blood cells ≥ 2000/μL
    b. Absolute neutrophil count ≥ 1500/μL (1.5×10^9/L)
    c. Hemoglobin ≥ 9.0 g/dL (90 g/L)
    d. Platelet count ≥ 100×10^9/L
    e. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (except patients with Gilbert Syndrome, who must have total bilirubin < 3.0 mg/dL)
    f. Alanine aminotransferase (ALT) ≤ 3 × ULN
    g. Aspartate aminotransferase (AST) ≤ 3 × ULN
    h. Serum creatinine ≤ 1.5 × ULN (133 μmol/L) OR calculated creatinine clearance ≥ 50 mL/min (using Cockcroft-Gault formula and actual body weight)
10. A documented left ventricular ejection fraction (LVEF) > 45% using standard echocardiogram or multigated acquisition (MUGA) scan test.
11. Reproductive Status
    a. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 14 days prior to the start of study treatment.
    b. Women must not be breastfeeding
    c. WOCBP must agree to follow instructions for methods of contraception for the duration of treatment with study treatment and for 5 months after bempegaldesleukin and/or nivolumab treatment completion. Women should use effective methods of contraception as indicated in Appendix 4. WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this protocol.
    d. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with bempegaldesleukin and 3 months after bempegaldesleukin treatment completion. In addition, male patients must be willing to refrain from sperm donation during this time.
12. Patients must be able and willing to comply with the study visit schedule and study procedures.

4.2 Exclusion Criteria

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

1. Use of an investigational agent or an investigational device within 28 days before randomization.
2. Female patients who are pregnant or lactating, who plan to get pregnant, or who have a positive serum or urine pregnancy test.
3. History of ocular/uveal melanoma or mucosal melanoma.
4. Active, known or suspected autoimmune disease. Patients with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
5. Conditions requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
6. Prior therapy for melanoma. Exceptions include surgery for the melanoma lesion(s) and/or adjuvant radiation therapy for CNS lesions at least 28 days prior to randomization. Patients must have recovered from all Grade ≥ 2 radiation-related toxicities.
7. Prior therapy with interferon, talimogene laherparepvec (Imlygic®), IL-2 directed therapy, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways).
8. History of leptomeningeal disease.
9. History of hypersensitivity or allergy to study drug components (for nivolumab, bempegaldesleukin, or any of their excipients).
10. History of severe hypersensitivity reaction to any monoclonal antibody.
11. Prior malignancy active within the previous 3 years **except for locally potentially curable cancers that have been apparently cured**, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast. Consult with the Medical Monitor about prior melanoma or other potential exceptions.
12. History of allogeneic stem cell transplant; history of solid organ or tissue transplant that requires systemic use of immune suppressive agents.
13. Prior surgery that required general anesthesia within 28 days before the first dose of study treatment; surgery requiring local/epidural anesthesia within 72 hours before first dose.
14. Active infection requiring systemic therapy within 14 days prior to randomization.

15. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on Screening chest computed tomography (CT) scan.
16. Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus (e.g., hepatitis B surface antigen [HBsAg, Australia antigen] positive, or hepatitis C antibody [anti-HCV] positive [except if HCV-RNA negative]).
17. Any positive test result for immunodeficiency or active human immunodeficiency virus (HIV-1/2 antibodies).
18. Prolonged Fridericia's corrected QT interval (QTcF) > 450 ms for men and > 470 ms for women at Screening.
19. Unstable or deteriorating cardiovascular disease within the previous 12 months prior to Screening including, but not limited to, the following:
    a. Unstable angina or myocardial infarction
    b. Congestive heart failure (New York Heart Association Class III or IV)
    c. Uncontrolled clinically significant arrhythmias
20. Transient ischemic attack (TIA) or CVA within 12 months prior to Screening
21. Need for > 2 antihypertensive medications for management of hypertension (including diuretics). Patients with hypertension must be on a stable antihypertensive regimen for the 14 days prior to randomization.

    Note: An antihypertensive medication that contains 2 drugs under one formulation is counted as 2 antihypertensive medications (e.g., angiotensin-converting-enzyme [ACE] inhibitor plus diuretic, calcium channel blocker plus ACE inhibitor).
22. History of pulmonary embolism, deep vein thrombosis, or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event (e.g., internal jugular vein thrombosis) within 3 months prior to randomization.

    Note: Patients with a history of a venous or arterial thromboembolic event must be asymptomatic for at least 2 weeks prior to randomization and must be receiving a stable regimen of therapeutic anticoagulation (preferably low molecular weight heparin [LMWH] or direct oral anticoagulation [DOAC]; see Section 5.13.2.3 for further guidance).

    Note: Unless there is a new medical contraindication observed after Cycle 1 Day 1, a patient with a history of venous or arterial thromboembolic event must be maintained on therapeutic anticoagulation throughout participation on the treatment phase of the study.
23. Patients with inadequately treated adrenal insufficiency.
24. Patients who have received a live/attenuated vaccine within 30 days of randomization.

25. Known current drug or alcohol abuse.
26. Receiving any medication prohibited in combination with study treatments as described in the respective product labels, unless medication was stopped within 7 days prior to randomization.
27. Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results (e.g., a condition associated with diarrhea or acute diverticulitis).

5.0 INVESTIGATIONAL PLAN

5.1 Study Design

This is a multicenter, randomized, open-label, Phase 3 study that will evaluate the efficacy and safety of bempegaldesleukin plus nivolumab compared with nivolumab after complete resection of melanoma in patients at high risk for recurrence.

Approximately 950 patients with completely resected Stage IIIA (LN metastasis > 1 mm), IIIB/C/D, or IV (AJCC 8th edition) NED cutaneous melanoma will be randomized in a 1:1 ratio between two treatment arms:

- Arm A: bempegaldesleukin plus nivolumab IV infusion q3w (see Table 8)
- Arm B: nivolumab IV infusion q4w (see Table 8)

Randomization will be stratified by:

- PD-L1 status by Dako PD-L1 PharmDx 28-8 assay: ≥ 1% vs < 1% vs indeterminate/not evaluable

  Note: PD-L1 indeterminate/not evaluable will be capped at a maximum of 25% of the total patient population.
- Stage: IIIA (LN metastases > 1 mm)/IIIB vs IIIC vs IIID/IV

Figure 1 displays the study schematic and the study procedures are presented in the Schedules of Events as follows:

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

5.2 Screening Period

Patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. For adolescent patients unable to give their written consent, in accordance with local regulations, one or both parents, a guardian, or a legally acceptable representative must be informed of the study procedures and must document permission by signing the ICF approved for the study prior to clinical study participation. Each patient must be informed about the nature of the study to the extent compatible with his or her understanding. Should a patient become capable or reach the age of majority, his or her consent should be obtained as soon as possible. The explicit wish of a patient who is a minor or unable to give his or her written consent, but

who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the Investigator. Minors who are judged to be of an age of reason as determined by local requirements should also give their assent. The assent should be documented based on local requirements. Continued assent should be documented when important new information becomes available that is relevant to the patient's assent.

After signing the ICF, patients will be enrolled using the Interactive Response Technology (IRT) and evaluated for entry criteria during the Screening period based on the assessments outlined in Section 1.2. Rescreening after screen failure will be allowed once. If rescreened, the patient must be reconsented.

Prior to randomization, the pathology reports must be reviewed by the Investigator and provided to the Sponsor. Pathology and staging source documentation at a minimum should include:

1) Primary site of disease
2) Breslow thickness
3) Ulceration status
4) Negative surgical margins, when applicable
5) Positive sentinel lymph node biopsy results
6) Size (mm) of lymph node involvement
7) Total number of tumor-involved regional lymph nodes
8) Presence of in-transit, satellite or microsatellite disease
9) Histological subtype
10) Site(s) of metastatic disease (for Stage IV only)
11) LDH (for Stage IV only)

Note: For patients who have undergone completion lymph node dissection, number of positive lymph nodes and total nodes resected should also be reported.

Note: Patients with melanoma recurrence after the initial wide local excision and sentinel lymph node biopsy are eligible only if the pathology of their nodal or in-transit resection at the time of the recurrence surgery meets the study entry stage criteria.

5.2.1 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 publishing requirements, as applicable, and to respond to queries from Regulatory Authorities.

Rescreening after screen failure will be allowed one time for a patient who has discontinued the study as a pretreatment failure (i.e., patient has not been randomized/ has not been treated). If rescreened, the patient must be reconsented.

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.

5.3 Treatment Period

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

Patients will be treated up to approximately 1 year (maximum of 17 cycles for Arm A and 13 cycles for Arm B) or until disease recurrence, death, unacceptable toxicity, symptomatic deterioration, decision by Investigator to discontinue treatment, decision by patient to discontinue treatment or withdraw consent from the study, patient is lost to follow-up, or decision by Sponsor to terminate the trial. Note: If cycles are delayed, treatment may continue beyond 1 year in order to complete 17 cycles for Arm A or 13 cycles for Arm B.

Study treatment is administered q3w (Arm A) or q4w (Arm B), and patients will have clinic visits for dose administration and/or study assessments approximately 3 times a month (see Table 2 for Arm A and Table 3 for Arm B details). If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation.

5.3.1 Description of Study Drugs

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

Table 7: Description of Study Drugs

5.3.2 Administration of Study Treatments

The first dose of study drug should be administered within 5 calendar days following randomization. Table 8 provides the timing of study drug administration.

Table 8: Selection and Timing of Dose

Treatment Arm	Study Treatment	Starting Dose	Frequency of Administration	Route of Administration
Arm A[a]	Bempegaldesleukin (NKTR-214)	0.006 mg/kg[b]	q3w	IV
	Nivolumab	360 mg or 4.5 mg/kg if < 40 kg[c]	q3w	IV
Arm B	Nivolumab	480 mg or 6.0 mg/kg if < 40 kg[c]	q4w	IV

IV = intravenous; q3w = every 3 weeks; q4w = every 4 weeks.

a. Bempegaldesleukin dose is based on IL-2 content. Bempegaldesleukin will be administered before nivolumab. Nivolumab administration should start at least 30 minutes from the end of bempegaldesleukin administration.

b. Bempegaldesleukin may be held or reduced to 0.003 mg/kg based on observed treatment-related toxicities (Section 5.10.1.1). If the bempegaldesleukin dose is reduced to 0.003 mg/kg, the dose should remain at this level throughout the remainder of the study and cannot be re-escalated.

c. The lower dose is for patients who are < 40 kg. Nivolumab may be held based on observed treatment-related toxicities; no dose adjustments for treatment-related toxicities are allowed (Section 5.10.1.2).

5.3.2.1 Assessment of Hydration and Renal Function

Hydration and renal function must be assessed within 24 hours prior to study drug administration, or as soon as locally feasible, by a local laboratory (see Appendix 1B for the list of analytes that require collection and evaluation prior to bempegaldesleukin study drug administration). For patients who must delay study treatment due to creatinine increase, see additional information regarding criteria to delay (Section 5.10.1.1 and Section 5.10.1.2), resume (Section 5.10.3), or permanently discontinue study treatment (Section 5.12). Underlying reasons for decreased oral intake (such as nausea) should be addressed and treatment (such as IV hydration) should be provided.

5.3.2.2 Bempegaldesleukin Dosing

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

Bempegaldesleukin will be administered before nivolumab. Bempegaldesleukin will be administered as an IV infusion over approximately 30 minutes (exclusive of the flush time) at a starting dose of 0.006 mg/kg q3w (± 3 days). After the bempegaldesleukin IV infusion is administered, flush the IV line with an appropriate amount of diluent (e.g., 0.9% Sodium Chloride or 5% Dextrose in Water) to ensure that the complete dose is administered. Nivolumab administration should start at least 30 minutes from the end of the bempegaldesleukin administration. Patients may be dosed no less than 18 days from the previous dose.

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 5.11.5. 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 5.10. In the event that nivolumab is permanently discontinued due to toxicities, see Section 5.12. There will be no dose escalations of bempegaldesleukin allowed. Bempegaldesleukin treatment can continue for patients randomized to the bempegaldesleukin and nivolumab combination arm in the event that nivolumab is permanently discontinued due to toxicities (see Section 5.12.1).

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

5.3.2.3 Arm A and Arm B: Nivolumab Dosing

Patients in Arm A should receive nivolumab at a dose of 360 mg (or 4.5 mg/kg for patients < 40 kg) over an approximately 30-minute IV infusion on Day 1 of each treatment cycle q3w (± 3 days). If needed, flush the IV line with an appropriate amount of diluent (e.g., 0.9% Sodium Chloride or 5% Dextrose in Water) after the nivolumab infusion. Nivolumab should be given at least 30 minutes after the completion of the bempegaldesleukin infusion.

Patients in Arm B should receive nivolumab at a dose of 480 mg (or 6.0 mg/kg for patients < 40 kg) as an IV infusion on Day 1 of each treatment cycle q4w (± 3 days). Nivolumab should be infused over approximately 30 or 60 minutes, according to the recommended infusion time specified in the approved country-specific nivolumab label. If needed, flush the IV line with an appropriate amount of diluent (e.g., 0.9% Sodium Chloride or 5% Dextrose in Water) after the nivolumab infusion.

For patients < 40 kg, nivolumab dosing will be determined by the patient's weight in kilograms, which will be determined before the start of each cycle. If the patient's weight is within 10% of the Cycle 1 Day 1 weight, the study drug doses do not need to be recalculated depending on institutional guidelines/preference. If the patient's weight has changed > 10% from the Cycle 1 Day 1 weight, the dose of nivolumab must be recalculated and subsequent weight measurements should be compared with this new baseline weight to determine if further nivolumab dose recalculations are necessary.

Note: If a patient's weight fluctuates throughout the course of treatment, administer nivolumab based on the patient's weight at time of dosing. For example, if the patient's baseline weight is 42 kg, the patient will be dosed with 480 mg of nivolumab if the patient is on Arm B. At a later subsequent cycle, if the patient's weight falls to 38 kg, the patient will be administered 6.0 mg/kg.

There will be no dose escalations or reductions of nivolumab allowed; however, dose modification due to weight change will be allowed. In Arm A, patients may be dosed no less than 18 days from the previous dose during q3w cycles. In Arm B, patients may be dosed no less than 25 days from the previous dose during q4w cycles.

Patients should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, patients should be managed according to directions in Section 5.11.5.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the patient tolerates the treatment (see Section 5.10.1.2). In the event that bempegaldesleukin is permanently discontinued due to toxicities (see Section 5.12.1), patients may continue on nivolumab alone.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Please refer to the nivolumab Pharmacy Manual for additional information on nivolumab IV administration.

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

5.3.3 Monitoring, Vital Signs, and Hydration Guidelines

The study site must be equipped for medical emergencies. Study agent(s) should be administered in an area with access to resuscitation equipment.

5.3.3.1 Frequent Vital Signs

Refer to Section 8.18 for vital sign measurements, which are to be monitored according to the Schedule of Events (Section 1.2).

5.3.3.2 Hydration Guidelines

Important safety information and hydration instructions are to be provided to patients. Hydration and renal function should be assessed within 24 hours prior to study drug administration or as soon as locally feasible (see Section 5.3.2.1). 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 handout.

Adult Hydration Guidelines:

For adult patients randomized to bempegaldesleukin in Arm A, administer at least 1 liter of IV fluid on bempegaldesleukin dosing days (Day 1 of each cycle). For the next 3 days (Days 2 to 4) after administration of bempegaldesleukin, patients are to be instructed to drink at least 2 liters per day of self-administered oral hydration (Table 9). (Note: For time points where PK samples are collected, it is preferable to collect PK samples before administering IV fluid.)

Adolescent Hydration Guidelines:

Hydration guidance for adolescent patients is weight-based. Adolescents who weigh more than 40 kg follow the Adult Hydration Guidelines. For adolescent patients who weigh less than 40 kg randomized to Arm A, administer 500 mL of IV fluid on bempegaldesleukin dosing days (Day 1 of each cycle). For the next 3 days after administration of bempegaldesleukin (Days 2 to 4), adolescents < 40 kg are to be instructed to drink at least 1 liter of fluids per day (Table 9). (Note: For time points where PK samples are collected, it is preferable to collect PK samples before administering IV fluid.)

Table 9: Hydration Guidelines for Adults and Adolescents

	Adults & Adolescents ≥ 40 kg	Adolescents < 40 kg
Day of infusion (IV)	1000 mL per day	500 mL per day
Days 2-4 (Oral)	2000 mL per day	1000 mL per day

IV = intravenous.

Hydration Guidelines for All Patients:

Advise patients to refrain from activities that may contribute to dehydration (including, but not limited to, strenuous activity, long hot showers, and saunas) for Days 1 to 4 following each bempegaldesleukin administration. Advise patients with orthostatic symptoms to call their treating oncologist and consider increasing oral hydration.

For Cycles 1 and 2, site personnel must contact the patient (by telephone or clinic visit) at least once between Days 3 and 5, inclusive, 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 administration of bempegaldesleukin in Cycles 3 to 17, 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 (e.g., evidence of fluid overload).

5.3.4 Duration of Treatment

Patients will remain on treatment until:

- Disease recurrence (local, regional or distant), including new primary melanoma (except for MMIS Stage 0)

  Note: Non-melanoma skin cancer does not require treatment discontinuation.
- Death
- Unacceptable toxicity
- Completion of up to approximately 1 year of study treatment (maximum of 17 cycles for Arm A and 13 cycles for Arm B)
- Symptomatic deterioration
- Investigator's decision to discontinue treatment
- Patient decision to discontinue treatment

- Patient withdraws consent for further treatment
- Patient is lost to follow-up
- Sponsor decides to terminate the study
- Meets any other discontinuation criteria listed in Section 5.12

5.3.5 Treatment Compliance

Patients will receive study drug at the study site directly from the Investigator or designee, under medical supervision. The date and time of each study drug dose administered in the clinic will be recorded in the source documents and recorded in the case report form (CRF). The dose of study drug and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering study drug.

For patients receiving bempegaldesleukin: between Days 3 and 5 (inclusive) following the first 2 infusions of bempegaldesleukin, site personnel must contact the patient to assess compliance with the oral hydration guidelines (see Section 5.3.3.2).

5.4 Discontinuation from Study Treatment

Patients may choose to discontinue study treatment at any time, for any reason, and without prejudice to further treatment. Patients may discontinue treatment of all or one of the study drugs based on AEs (see Section 5.12).

Study treatment discontinuation criteria are listed in Section 5.12.

In the event of a patient's decision to discontinue treatment, the Investigator will make every effort to complete the Long-Term Follow-up Schedule of Events (Table 4).

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

In the event of early termination of the study, patients on treatment will be offered standard of care dosing for up to a total of 1 year for nivolumab (which includes nivolumab already administered as part of the clinical trial protocol), or until one of the following criteria is met, whichever occurs first:

- Unacceptable toxicity
- Disease recurrence
- Investigator discretion

5.5 Long-Term Follow-up

Long-term follow-up comprises 2 Safety Follow-up Visits and Survival Follow-up visits. Long-term follow-up will continue until the patient withdraws consent, dies or is lost to follow-up, or the study is terminated by the Sponsor. Assessments should continue as described in the Long-Term Follow-up Schedule of Events (Table 4).

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.

For patients who discontinue study treatment before BICR-confirmed disease recurrence, imaging assessments will continue to be collected as described in Section 7.1.

5.5.1 Safety Follow-up

- Safety Follow-up Visit 1 should occur 30 (± 7) days after the last dose of all study drug(s), or at the time the decision is made to discontinue treatment if discontinuation is after the Safety Follow-up Visit 1 window or before a new antineoplastic regimen starts.
- Safety Follow-up Visit 2 occurs 100 (± 7) days after the last dose of all study treatment(s).
- Safety Follow-up Visits should occur regardless of initiation of subsequent anticancer therapy.
- Both Safety Follow-up Visits should be conducted in person.
- Per clinical judgment, the patient may come in earlier for additional follow-up.
- For AE and SAE reporting periods, please refer to Sections 8.5 and 8.7.

5.5.2 Survival Follow-up

The Sponsor may request that survival data be collected on all treated/randomized patients outside of the protocol-defined window (Section 1.2). At the time of this request, each patient will be contacted to determine their survival status unless the patient has withdrawn consent for all contacts or is lost to follow-up. Survival follow-up and patient participation in the study will continue until death, the patient withdraws consent from all further study assessments including survival follow-up, is lost to follow-up, or study termination by the Sponsor.

- All patients will be contacted for survival every 12 weeks (± 14 days) following Safety Follow-up Visit 2 (or 100 [± 7] days after last dose of study treatment). Survival Follow-up may be conducted in person or by telephone. Alternative methods to determine survival status may be used (e.g., access to medical records and public record searches) as allowed by local regulations and/or guidelines.

- Information about subsequent cancer therapy will also be collected during these contacts. 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 may be collected.
- Safety follow-up: Please refer to Section 8.5 and Section 8.7 for details on requirements for safety follow-up that may apply during Survival Follow-up.

5.6 End of Study

The study will be considered complete when the last patient's last visit has been conducted and the data is mature for OS analysis. See Section 5.5 about details for collection of survival data. In the event of early termination of the study, patients on treatment will be offered standard of care dosing for up to a total of 1 year for nivolumab (which includes nivolumab already administered as part of the clinical trial protocol), or until one of the following criteria is met, whichever occurs first:

- Unacceptable toxicity
- Disease recurrence
- Investigator discretion

5.7 Pharmacokinetic and Immunogenicity Measurements

PK and immunogenicity assessment data will be collected from study patients assigned to the nivolumab + bempegaldesleukin and nivolumab arms at the time points indicated in Table 10.

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 immunogenicity sampling should be adjusted accordingly. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. All predose samples should be collected within 24 hours before the start of any dose infusion. Draw blood samples from a site other than the infusion site (i.e., contralateral arm) on days of infusion.

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

For adolescent patients < 40 kg, local standards for volumes of blood based on body weight that may be drawn within a specific time period should be followed. In order to obtain the samples required for safety, PK, and pharmacodynamic evaluations specified at a time point, blood

volumes for safety laboratory analysis should be minimized through the use of pediatric sample tubes, if possible. In case, despite using these measures, the blood volumes required in the Schedule of Events for a time point will exceed those recommended for the patient, the Sponsor should be contacted for instructions on which blood tests can be omitted or modified to meet volume requirements. These omitted/modified tests will likely be pharmacodynamic and/or PK assessments since all required safety assessments must be performed.

Serum PK samples will be analyzed for nivolumab by a validated ligand-binding assay. Plasma PK samples will be analyzed for NKTR-214-RC (bempegaldesleukin-related molecules; mixture of compounds containing IL-2 independent of PEG conjugation status) and Total-PEG (mixture of compounds containing PEG independent of conjugation status to IL-2) by validated ligand-binding assays as well as NKTR-214-AC (active bempegaldesleukin-related molecules; mixture of 2-PEG-IL-2, 1-PEG-IL-2, and free IL-2) by a qualified ligand binding assay. The Cycle 1 Day 8 NKTR-214 PK blood sample may also be used to assess inflammatory cytokines (biomarkers; [redacted]).

Validated methods to detect anti-bempegaldesleukin, anti-PEG, anti-IL-2 and anti-nivolumab anti-drug antibodies (ADA) will be used to analyze 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 (ECLAs). Putative positive samples for anti-bempegaldesleukin, anti-IL-2 and anti-nivolumab ADA will then be analyzed in competition ECLAs to confirm positivity. Confirmed anti-bempegaldesleukin ADA-positive samples will be tested further in 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 each assay (anti-nivolumab, anti-bempegaldesleukin and anti-IL-2) will then be tested to obtain a titer. Samples confirmed to be positive for anti-bempegaldesleukin, anti-IL-2 and anti-nivolumab ADA may also be tested for neutralizing activity for IL-2 and nivolumab using validated cell-based assays.

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

[redacted]

For all PK and immunogenicity 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 10: Pharmacokinetic and Immunogenicity Sampling for Arm A and Arm B

Study Day of Sample Collection[a]	Event	Time (Relative to Start of Bempegaldesleukin Infusion) Hour:Min	Arm A				Arm B	
			Bempegaldesleukin		Nivolumab		Nivolumab	
			PK Blood Sample[f]	IMG Blood Sample	PK Blood Sample	IMG Blood Sample	PK Blood Sample	IMG Blood Sample
Cycle 1 Day 1	Predose	00:00	X	X	X	X	X	X
	EOI[b]	00:30	X					
		4:00[c]	X					
Cycle 1 Day 3[d]		48:00[d]	X					
Cycle 1 Day 5[e]		96:00[e]	X					
Cycle 1 Day 8[f]		168:00[f]	X					
Cycle 2 Day 1	Predose	00:00	X	X	X	X	X	X
Day 1 of Cycles 5, 9, 13, and 17	Predose	00:00	X	X	X	X		
Day 1 of Cycles 4, 7, 10, and 13	Predose	00:00					X	X
Safety Follow-up 1		30 (± 7) days from last dose of all study drug(s), or at time of permanent treatment discontinuation if it is after the Safety Follow-up Visit 1 window or before a new antineoplastic regimen starts		X	X	X	X	X
Safety Follow-up 2		100 (± 7) days from the last dose of all study treatment(s)		X	X	X	X	X

EOI = end of infusion; IMG = immunogenicity; PK = pharmacokinetic.

a. If a patient permanently discontinues study drug treatment during the sampling period, they will move to sampling at the follow-up visits.

b. This sample should be taken immediately prior to completion of the bempegaldesleukin administration (preferably within 2 minutes prior to the end of administration). EOI 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. Sample can be collected ± 1 hour but is preferred as close to 04:00 hours as is clinically feasible.

d. If patients are dosed on Thursday, Day 3 sample can be collected 24 to 48 hours postdose. Samples can be collected ± 3 hours.

e. Day 5 sample can be collected ± 1 day.

f. Cycle 1 Day 8 sample can be collected ± 1 day.

Note: All predose samples should be collected within 24 hours before the start of any dose infusion. For time points where IV fluid hydration is administered, it is preferable to collect the PK sample before IV fluid administration.

5.8 Biomarkers

Various factors that could potentially predict clinical response and incidence of AEs to treatment with nivolumab in combination with bempegaldesleukin will be investigated in peripheral blood and in pre-, on-treatment, and upon recurrence tumor specimens.

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

Any remaining tissue collected for this study will be used for additional research to further understand and investigate the mechanism of action and relapse of disease in patients treated with nivolumab in combination with bempegaldesleukin (see Section 5.8.3). Also, the samples will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment, etc.

[redacted]

Table 11: Biomarkers Collection Schedule for Arm A and Arm B

Collection Timing[a]	Tissue Collection[b]	[redacted]		[redacted]		CVA or TIA Biomarker[e]	
	Arm A and B	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
Screening[f]	X						
Cycle 1 Day 1 (predose)		X	X	X	X	X	X
Cycle 1 Day 8		X	X				
Cycle 2 Day 1 (predose)		X	X		X		
Cycle 3 Day 1 (predose)				X			
Cycle 4 Day 1 (predose)					X		
Cycle 5 Day 1 (predose)				X		X	X
Cycle 6 Day 1 (predose)					X		
Cycle 8 Day 1 (predose)				X			
Upon Disease Recurrence[f]	X	X	X	X	X		
New CVA or TIA Event[g]						X	X
30 Days Post CVA or TIA Event (± 7 days)						X	X
Grade 3 Treatment-Related AE Resulting in Dose Delay[h]	X[i]	X	X	X	X		

AE = adverse event; [redacted] CVA = cerebrovascular accident; [redacted]; TIA = transient ischemic attack.

a. Biomarker sampling that occurs prior to dosing of study drug can occur within ± 3 days from the scheduled time.

b. See Section 5.8.1.

c. See Section 5.8.2.3. Omit for adolescents < 40 kg.

d. See Section 5.8.2.2.

e. See Section 5.8.2.4. The sample at 30 days post CVA or TIA event may be collected at Safety Follow-up Visit 1 if within 30 days (± 7 days) after CVA or TIA event.

f. Tumor tissue required during Screening; upon disease recurrence, tumor sample collection is optional but highly recommended.

g. Blood samples should be collected as close to the new CVA or TIA event as feasible.

h. See Section 5.8.2.1.

i. If a biopsy of the affected organ is performed for assessment of the AE, it is strongly recommended to collect a tissue specimen for biomarker analysis.

Note: All predose samples should be collected within 24 hours before the start of any dose infusion.

5.8.1 Tissue Collection

5.8.1.1 Tumor Tissue Collection

Tumor tissue must be provided during Screening to allow for patient enrollment into the study. Tumor tissue from either the biopsy, the resected primary tumor or metastatic lymph nodes is acceptable; however, the most recently obtained resected primary tumor tissue is preferred. A formalin-fixed paraffin-embedded (FFPE) block obtained prior to randomization (collected within 6 months prior to randomization and with no intervening treatment) from the most recently resected site of disease must be submitted. If a block is not available, a minimum of 15 unstained slides, preferably 30 slides (that have been sectioned within the 4 months prior to randomization) may be submitted. If 15 unstained slides are not available, please contact the Medical Monitor.

Tumor tissue will be stained for expression of PD-L1. PD-L1 expression will be assessed by a pathologist and membranous PD-L1 expression scored in tumor cells if a minimum of 100 evaluable tumor cells are present. Central PD-L1 testing (Dako PD-L1 PharmDx 28-8 immunohistochemical assay) is mandatory. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 expression ≥ 1%, PD-L1 expression < 1%, indeterminate, or not evaluable based on the frequency of tumor cell surface PD-L1 staining. Samples that have < 100 evaluable cells are considered not evaluable. Where membrane staining is obscured by high cytoplasmic staining, but the tumor tissue sample contains the minimum number of evaluable tumor cells, samples will be deemed PD-L1 indeterminate.

Tumor tissue may also be used to assess other putative predictive biomarkers of nivolumab and bempegaldesleukin efficacy and/or to better characterize the tumor-immune microenvironment. Various molecular markers with potential predictive value for the treatment of melanoma with nivolumab, bempegaldesleukin, and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers may include but are not limited to tumor-infiltrating lymphocytes or subpopulations of tumor-infiltrating lymphocytes, macrophages, B-cells, cytokines and chemokines, markers of inflammation, mutations, and mRNA expression signatures.

5.8.1.2 Other Tissue Collection

Upon occurrence of a Grade ≥ 3 treatment-related AE that results in a dose delay, if a biopsy of the affected organ is performed, it is strongly recommended that a tissue specimen for biomarker analysis be collected. These particular non-tumor biopsies are prepared preferably by flash/snap freezing, but if this cannot be done by the site, FFPE biopsies are also acceptable. These samples may be used for the assessment of immune cell markers, soluble analytes (e.g., cytokines, chemokines), including but not limited to T cell, regulatory cell, and natural killer cell markers, as well as for the expression of major histocompatibility complex class I/II molecules.

5.8.2 Peripheral Blood Biomarkers

A variety of biomarkers that may predict or impact the treatment efficacy with bempegaldesleukin and nivolumab will be investigated in peripheral blood specimens taken from all patients prior to and during treatment. Several analyses will be completed and are described briefly below. Additional biomarker assessments may also be performed if samples are available.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.8.3 Sample Collection and Storage

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

For All US sites:

Additional research participation is required for all investigational sites in the US. If the IRB and investigative site agree to the mandatory additional research retention and/or collection, then the study patient must agree to the mandatory additional research collection as a requirement for participation in the study.

For Non-US Sites:

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

The use of residual samples for additional research is intended to expand the translational research and development capability at the Sponsor and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

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.

5.9 Health-Related Quality of Life (HRQoL)

Available therapies (e.g., interferon alpha) to treat patients with resected Stage IIIA (LN metastasis > 1 mm)/B/C/D and IV melanoma are associated with substantial toxicities and unclear clinical benefit. The evaluation of PROs in oncology clinical trials is becoming increasingly important to understand the benefits and risks of treatment from a patient perspective. However, PRO data from investigational trials in this population are lacking.

The EORTC QLQ-C30 will be used to assess changes from baseline in PROs during and after treatment. The GH/QoL and physical functioning subscales define secondary endpoints as they measure constructs deemed relevant to the population and have been prioritized by regulatory agencies and payers. The EQ-5D-5L will be used to assess general health status and capture data to calculate utilities for economic modeling.

Patients who are ≥ 18 years of age at the time of informed consent will be asked to complete the EORTC QLQ-C30 followed by the EQ-5D-5L before any other study-related procedures are performed as outlined in Section 1.2. Paper forms should be used when patients are in the clinic and phone script should be used when patients are in follow-up. Refer to Section 7.4 for additional information.

5.10 Dosage Modification

If bempegaldesleukin or nivolumab meet the criteria for dose delay, then administration of both drugs must be delayed until the criteria to resume are met (Section 5.10.3).

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

Patients who require a dose delay of nivolumab or bempegaldesleukin should be re-evaluated weekly or more frequently if clinically indicated and should resume treatment with combination of bempegaldesleukin and nivolumab when retreatment criteria are met (Section 5.10.1). Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Bempegaldesleukin and nivolumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

Discontinuation criteria for bempegaldesleukin and nivolumab are provided in Section 5.12.

5.10.1 Dose Delay and Reduction Criteria

5.10.1.1 Arm A: 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 treatment-related toxicities. Medical Monitor consultation is required for dose reduction. If the bempegaldesleukin dose is reduced to 0.003 mg/kg, the dose level should remain at this level throughout the remainder of the study and cannot be re-escalated. If bempegaldesleukin meets the criteria for dose delay, then administration of both drugs (for patients on Arm A) must be delayed until the criteria to resume are met.

Bempegaldesleukin administration should be delayed or reduced for the following reasons:

- For persistent Grade 2 treatment-related AE
  - Definition of persistent Grade 2 treatment-related AE: A Grade 2 AE lasting at least 3 weeks and ongoing at the time of subsequent dosing that is attributed as either "possibly related" or "related" to bempegaldesleukin
  - Dose delay or dose reduction:
    - For the 1st or 2nd occurrence of the same persistent Grade 2 treatment-related AE, bempegaldesleukin administration should be delayed until the treatment-related AE resolves to Grade 1 or baseline, and the treatment-related AE should be treated symptomatically.
    - After the 1st occurrence, bempegaldesleukin may be continued at 0.006 mg/kg.
    - After the 2nd occurrence, bempegaldesleukin should be dose-reduced from 0.006 mg/kg to 0.003 mg/kg.
  - Treatment discontinuation: After the 3rd occurrence, discontinuation of bempegaldesleukin may be considered in consultation with the Medical Monitor.
  - Special cases
    - Persistent Grade 2 treatment-related AEs of constitutional and flu-like symptoms (fever, chill, myalgia/arthralgia) except fatigue and asthenia: please follow management guideline above, plus prophylactic medication (e.g., nonsteroidal anti-inflammatory drugs, antipyretic, antihistamine) should be considered. Persistent Grade 2 treatment-related AEs of fatigue and asthenia do not require dose delay or reduction.
    - For Grade 2 treatment-related AEs listed below, please see relevant protocol section for specific management guidelines.
      - Grade 2 treatment-related AEs except fatigue and asthenia (not applicable)
      - Creatinine increase (see Grade ≥ 2 creatinine increase below)

  - AST/ALT elevations (Section 5.10.2)
  - Elevated hepatic transaminases (Section 5.11.1)
  - Adrenal insufficiency and hypophysitis (Section 5.11.2)
  - Eosinophilia (Section 5.11.3)
  - Immune-mediated AE (Section 5.11.4)
  - Infusion-related reactions (Section 5.11.5)
  - Immediate infusion-related reactions, flu-like symptoms, and hypersensitivity events (Section 5.13.1)

- 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). Refer to renal AE management algorithm in the current nivolumab Investigator's Brochure for further guidance.
- Grade ≥ 3 AE at least possibly related to bempegaldesleukin: bempegaldesleukin must be delayed until resolution to Grade 1 or baseline (unless otherwise requiring permanent discontinuation, per Section 5.12.1), with the following exceptions:
  - Grade ≥ 3 lymphopenia
  - Grade ≥ 3 asymptomatic amylase or lipase elevation

Bempegaldesleukin dosing may resume at the same bempegaldesleukin dose or at a 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 (see Section 5.12.1 for permanent discontinuation criteria).

Note: For Grade ≥ 3 AEs that cause dose delay, if biopsy of AE-affected organ is conducted, tissue specimen for biomarker analysis is highly recommended (see Section 5.8.1). Five to 10 slides are recommended, with a minimum of 5 slides.

5.10.1.2 Arm A or Arm B: Nivolumab Dose Delay Criteria

If nivolumab meets the criteria for dose delay, then administration of both drugs (for patients on Arm A) must be delayed until the criteria to resume are met.

Nivolumab administration should be delayed for the following:

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

- Grade 3 skin, treatment-related AE
- Grade 3 treatment-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase and/or lipase abnormalities do not require dose delay
  - Grade ≥ 3 AST, ALT, total bilirubin will require dose discontinuation (unless satisfying the Cycle 1 AST/ALT elevation criteria outlined in Section 5.10.2)
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

Patients who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when retreatment criteria are met. Dose reductions for nivolumab are not permitted in this study.

5.10.2 Dose Modification Criteria for Bempegaldesleukin and Nivolumab for Cycle 1 ALT/AST Elevations

The following recommendations are for Cycle 1 only and are not intended to serve as rigid guidelines or to replace clinical judgment. Subsequent cycles should follow standard Hepatic Adverse Event Management Algorithm in the nivolumab Investigator's Brochure.

Rule out alternative etiologies. Consider imaging if obstruction is suspected. If there is a non-inflammatory etiology, treat accordingly and continue bempegaldesleukin and nivolumab.

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

AST or ALT > 3.0 to ≤ 5 × ULN (within first cycle of bempegaldesleukin plus nivolumab)

Increase frequency of liver function test monitoring to approximately every 3 days and delay treatment until lab abnormalities resolve to Grade 0 to 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 (within first cycle of bempegaldesleukin plus nivolumab)

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

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

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

- Discontinue bempegaldesleukin plus nivolumab

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

ALT or AST > 8.0 × ULN (follow Hepatic Adverse Event Management Algorithm in the nivolumab Investigator's Brochure)

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

Please refer to Section 5.12.1 for discontinuation criteria.

5.10.3 Criteria to Resume Bempegaldesleukin and/or Nivolumab

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

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients who have not experienced a Grade 3 treatment-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Patients with baseline Grade 2 AST/ALT and/or total bilirubin abnormalities may resume dosing when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Treatment-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible to resume study treatment if discussed and approved by Medical Monitor.
- Patients with treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor (or designee). Grade ≥ 3 adrenal insufficiency and/or Grade 4 hypophysitis require discontinuation regardless of control with hormone replacement (see Section 5.12.1 for permanent treatment discontinuation criteria). Hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should not require discontinuation.

- For patients who must delay study treatment due to Grade ≥ 2 creatinine increase due to a non-inflammatory cause (Section 5.10.1), delay retreatment with study drug for approximately 3 to 5 days. After the dosing delay, the patient may resume study drug when serum creatinine has returned to Grade ≤ 1, as assessed within 24 hours prior to redosing (or as soon as locally feasible), except where permanent discontinuation of study drug is required (Section 5.12.1).

5.11 Monitoring and Management of Adverse Events

5.11.1 Monitoring and Management of Elevated Hepatic Transaminases

Elevated hepatic transaminases are an overlapping toxicity that can occur for both bempegaldesleukin and nivolumab. The elevations in hepatic transaminases associated with bempegaldesleukin typically occur at the time of peak active cytokine concentration in the blood (Days 4 to 8) and are often accompanied by other IL-2 mediated AEs such as flu-like symptoms, rash or pruritus. The transient elevations in hepatic transaminases are usually asymptomatic, mild or moderate in severity, not associated with increased total bilirubin and alkaline phosphatase, resolve spontaneously without treatment, and predominantly occur in Cycle 1 and Cycle 2; the transaminase elevations are considered to occur in the context of IL-2 mediated AEs. For transaminase elevations occurring in Cycle 1 consistent with an IL-2 mediated cytokine-related effect without alternative etiologies, follow the Cycle 1 management guideline for ALT/AST elevations in Section 5.10.2.

Hepatic events, including elevated liver function tests, have also been observed for nivolumab. Most cases were of low or moderate severity. Higher grade abnormalities are concerning for immune-mediated hepatitis, and typically occur with a later onset (median time to onset of 3.3 months). Immune-mediated hepatitis generally results in a quick rise in liver function tests and responds to corticosteroids or immune-modulating agents. For transaminase elevations occurring in Cycle 2 onwards potentially involving an immune-mediated mechanism, follow the immune-mediated hepatic AE management guidelines in the nivolumab Investigator's Brochure or product labeling for appropriate management.

5.11.2 Monitoring and Management of Adrenal Insufficiency and Hypophysitis

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

5.11.3 Monitoring and Management of Eosinophilia

5.11.3.1 Bempegaldesleukin-Induced Eosinophilia

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

Absolute eosinophil count should be closely monitored per protocol. If a study patient is suspected to have eosinophilic disorder (symptoms may involve skin, lungs, digestive tract, heart, blood, and nervous systems) with absolute eosinophil count $\geq 5000/\mu L$ ($5 \times 10^9/L$) level, delaying bempegaldesleukin treatment may be considered while evaluating and treating the patient as clinically indicated.

5.11.3.2 Eosinophilic Disorders

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

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

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

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Bempegaldesleukin and nivolumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms including the use of systemic corticosteroids (see the nivolumab Investigator's Brochure) have been developed to assist Investigators in assessing and managing the following groups of AEs (including, but not limited to):

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis

A management algorithm for possible signs and symptoms of CVA for patients treated with bempegaldesleukin in combination with a checkpoint inhibitor is provided in Appendix 6.

5.11.5 Treatment of Bempegaldesleukin-Related or Nivolumab-Related Infusion Reactions

Infusion reactions have been reported during bempegaldesleukin and nivolumab infusions. If such a reaction were to occur with either the bempegaldesleukin or nivolumab infusion, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, myalgia, hypotension, hypertension, bronchospasm, or other hypersensitivity/allergic-like reactions. Infusion reactions should be graded as outlined below (consistent with Common Terminology Criteria for Adverse Events [CTCAE] version 5.0 grading of infusion-related reaction); please also refer to Section 8.3.

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

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

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

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

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

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

- Immediately discontinue infusion of bempegaldesleukin or nivolumab. Begin an IV infusion of normal saline and treat the patient as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
- The patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at the bedside and monitor the patient until recovery of the symptoms.

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

5.11.6 Management Algorithm for Cytokine Release Syndrome

Cytokine-release syndrome (CRS) is a clinical diagnosis with a constellation of symptoms often characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. In addition, diarrhea and end organ dysfunction can be seen in CRS. Many of these symptoms overlap with known AEs seen in bempegaldesleukin and nivolumab combination therapy (i.e., pyrexia and hypotension). These symptoms may be seen in infusion reactions as well as other known syndromes, such as tumor lysis syndrome and macrophage activation syndrome. For suspected CRS of Grade 3 or above, the Investigator is encouraged to contact the Sponsor. An algorithm for the management of CRS is provided in Appendix 7.

5.12 Discontinuation Criteria

Bempegaldesleukin combined with nivolumab treatment or nivolumab monotherapy must be permanently discontinued for the following:

- 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.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness. (Note: Under specific circumstances, a patient who has been imprisoned may be permitted to continue as a patient. Strict conditions apply and Sponsor approval is required.)

- 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.
- Noncompliance of the patient with protocol-mandated procedures based on the judgment and agreement of both the Investigator and Sponsor.
- See additional study treatment discontinuation criteria specific to bempegaldesleukin- or nivolumab-related AEs (Section 5.12.1).
- Termination of the study by the Sponsor.
- Disease recurrence (local, regional, or distant), including new primary melanoma (except MMIS Stage 0)

  Note: Non-melanoma skin cancer does not require treatment discontinuation. In the absence of intolerable toxicity, patients with diagnosed MMIS Stage 0 melanoma will be eligible to continue study treatment using the same dose and schedule for their original melanoma of up to approximately 1 year of study treatment starting from first dose, at the discretion of the Investigator.
- Lost to follow-up (defined as after three attempts at contact by phone followed by one attempt by sending a certified letter).

If a patient has not experienced disease recurrence following discontinuation of study drug(s), every effort should be made to continue to obtain radiographic tumor assessments as outlined in Section 7.1.

A patient may also be withdrawn from investigational product/study by the Sponsor, Regulatory Authorities, or IRBs/ IECs.

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

Refer to the Schedule of Events (Section 1.2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the Investigator must immediately, within 24 hours of awareness of the pregnancy, notify the Sponsor of this event. If a female patient becomes pregnant, administration of the study drug(s) must be discontinued immediately. Refer to Section 8.13.2 (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 (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

5.12.1 Discontinuation Criteria for Treatment-Related Toxicities

Patients meeting any of the following criteria will be required to permanently discontinue all assigned study drug(s). In Arm A, per Investigator assessment, treatment with bempegaldesleukin or nivolumab alone may continue if a toxicity meeting discontinuation criteria below is considered related to one and not the other study drug and once the criteria to resume treatment are met (Section 5.10.3).

Study treatment should be permanently discontinued for the following:

- Any Grade ≥ 2 treatment-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 8 weeks or requires systemic treatment.
- Any Grade ≥ 2 treatment -related pneumonitis or interstitial lung disease that does not resolve following dose delay and systemic steroids (also see Pulmonary Adverse Event Management Algorithm in the nivolumab Investigator's Brochure).
- For Grade ≥ 3 adrenal insufficiency or Grade ≥ 4 hypophysitis, treatment needs to be discontinued regardless of control with hormone replacement (Note: Hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should not require discontinuation).
- Any Grade ≥ 3 non-skin, treatment -related AE lasting > 7 days or recurs, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
  - Grade 3 treatment -related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 treatment -related endocrinopathies (excluding adrenal insufficiency and hypophysitis) adequately controlled with only physiologic hormone replacement do not require discontinuation.
  - Grade 3 treatment -related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 treatment -related thrombocytopenia > 7 days or associated with clinically significant bleeding requires discontinuation.
- In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the Investigator and the Medical Monitor/designee must occur. For IL-2 mediated ALT/AST elevations < 8.0 × ULN in Cycle 1 only, study treatment does not need to be discontinued (see Section 5.10.2).

- Any treatment -related liver function test abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm in the nivolumab Investigator's Brochure):
  - AST or ALT > 5 × ULN to 8 × ULN for > 2 weeks
  - AST or ALT > 8 × ULN
  - Total bilirubin > 5 × ULN
  - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN
- Grade 3 or 4 infusion reaction of any duration:
  - For Arm A: If infusion reaction occurs during the bempegaldesleukin infusion or prior to the nivolumab infusion, discontinuation of bempegaldesleukin is required.
  - For Arm A: If infusion reaction occurs during the nivolumab infusion or later, discontinuation of both bempegaldesleukin and nivolumab is required.
- Any Grade 4 treatment -related AE or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days.
  - Grade 4 lymphopenia or leukopenia ≤ 14 days in duration.
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to Grade < 4 or return to baseline within 7 days.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 treatment -related endocrinopathy AEs (except adrenal insufficiency or hypophysitis), such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids at ≤ 10 mg of prednisone or equivalent per day, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued treatment.
- Arm A only: Any new CVA event confirmed by diffusion-weighted imaging MRI, regardless of neurological symptoms (e.g., cryptogenic CVA) and for suspected TIA without clear alternative etiology (see Appendix 6)

5.13 Prior and Concomitant Medications

Recording of prior medications should include prior cancer treatments, previous radiation, and over-the-counter medications.

All medications (prescription and over-the-counter), vitamin, and/or subsequent anticancer therapy taken by the patient from Screening through Follow-up Visit 2 visit will be documented and recorded, including start and stop date, dose and route of administration, frequency, and indication. Medications taken for a procedure (e.g., biopsy) should also be included. All medications taken to treat an AE/SAE should be recorded through Follow-up Visit 2.

Details regarding IV hydration will be recorded.

5.13.1 Prophylaxis and Management of Symptoms Related to Immediate Infusion-Related Reactions (Including Flu-Like Symptoms and Hypersensitivity Events)

Prophylaxis for flu-like symptoms with either acetaminophen or ibuprofen 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.

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

5.13.2 Permitted Concomitant Medications

5.13.2.1 Effect of Bempegaldesleukin on Concomitant Medications

At the study dose levels, bempegaldesleukin is expected to cause mild to moderate increases in circulating cytokines, some of which are known to have the potential to decrease the activity of multiple enzymes (cytochrome P450 enzymes, hepatic flavin monooxygenases, UDP-glucuronosyltransferases, sulfotransferases, and glutathione S-transferases) and drug transporters, and the suppressive effects can be additive (Haas, 2005; Zidek, 2009). The increases in circulating cytokines generally occur from Day 3 to Day 7 postdose, coinciding with the PK time course of bempegaldesleukin-related active cytokines (NKTR-214-AC). Consequently, treatment with bempegaldesleukin may lead to decrease in clearance of drugs that are substrates of these Phase 1 and Phase 2 drug metabolizing enzymes, or drug transporters, from Days 3 to 7 postdose. The magnitude of potential drug interactions with bempegaldesleukin is unknown. The clinical management of concomitant medications during the period of bempegaldesleukin-induced increases in cytokines is similar to treatment guidelines in the setting of an acute inflammatory response. That is, due to the possibility of broad reductions in clearance pathways, drugs with narrow therapeutic indices should be replaced with alternative agents that are not prone to drug interactions, reduced, or withheld

from Days 3 to 7 after administration of bempegaldesleukin. For further guidance, the investigator should consult with the Medical Monitor.

5.13.2.2 Steroids

Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Patients with pre-existing adrenal impairment requiring corticosteroid supplementation may be at increased risk for hypotensive episodes during treatment with bempegaldesleukin. 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 (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Use of corticosteroids for the management of immune-mediated AEs as outlined in the nivolumab Investigator's Brochure is permitted. Short-term use of systemic corticosteroids or immunosuppressive medication is permitted if administered for AE treatment. Daily dosage of prednisone or equivalents must be ≤ 10 mg for study treatment to resume.

5.13.2.3 Thromboembolism Prophylaxis and Treatment

Patients with a higher risk of thromboembolic event, or a history of venous or arterial thromboembolism must be receiving a stable regimen of anticoagulation. Low molecular weight heparin (LMWH) at prophylactic doses (e.g., enoxaparin at 1 mg/kg or flat dose up to 80 mg/day) is the preferred anticoagulant that should be initially considered. Other options such as oral factor Xa inhibitors (Direct Oral Anticoagulants) including rivaroxaban, apixaban, or edoxaban can be used after consulting with the Sponsor Medical Monitor. Unless there is a new medical contraindication observed after Cycle 1 Day 1, patients with a history of a venous or arterial thromboembolic event must be maintained on therapeutic anticoagulation throughout the time on study treatment. Acetylsalicylic acid should not be combined with LMWH or DOAC due to an increased risk of hemorrhage.

Warfarin is permitted; however, therapeutic dosing should target a specific international normalized ratio (INR) that is stable for at least 4 weeks prior to randomization. Reduction of warfarin dose after starting study treatment should be considered due to the possibility of drug-drug interactions between warfarin and bempegaldesleukin in which the latter has the potential to down-regulate metabolizing enzymes for warfarin. Frequent monitoring of INR and ongoing consideration of dose adjustments are warranted throughout the patient's participation on study, as bempegaldesleukin can down-regulate metabolizing enzymes for warfarin for approximately 1 week after administration of each dose of bempegaldesleukin.

5.13.2.4 Other Supportive Care

Bisphosphonates and RANK-L inhibitors are allowed for osteoporosis.

Live/attenuated vaccines are not allowed prior to or during the study. Vaccination with inactivated viruses is permitted consistent with the institutional guidelines. Allow appropriate time interval between the most recent study treatment administration and the next date of study treatment. If the patient experiences side effects after the flu vaccine or another inactivated vaccine, please manage study treatment administration per protocol guideline.

5.13.3 Prohibited and/or Restricted Concomitant Medications

5.13.3.1 Prohibited Medications

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.13.2) defined as a daily dose of greater than 10 mg prednisone equivalents
- Any concurrent systemic antineoplastic therapy for the treatment of melanoma or a new malignancy (except as noted). Patients who develop a new non-melanoma fully resectable malignancy (examples include but are not limited to: in situ bladder cancer, in situ gastric cancer, or in situ colon cancers; in situ cervical cancers/dysplasia; or breast carcinoma in situ; or prostate carcinoma) during the study may continue receiving study drugs if the only therapy required is hormonal therapy, surgery and/or radiation (and the surgery or radiation site does not overlap with a previous primary melanoma or melanoma metastasis location). Consultation with the Medical Monitor is required once a new malignancy is detected.
- Any live / attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella or Flumist® Quadrivalent) during treatment and until 100 days post last dose of nivolumab. Note: All vaccines available as of the date of this document against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19) are allowed on treatment. For any questions about COVID vaccines, please contact the Medical Monitor.

5.13.3.2 Blood Pressure Medications

Consideration should be given to withholding antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (e.g., alpha blockers for benign prostatic 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 on medications with antihypertensive effects for the treatment of coronary artery disease (CAD) (e.g., β-blockers, Ca channel blockers, nitrates, etc.) should be able to withhold these drugs prior to initiation of treatment. Other medications (e.g., for erectile dysfunction) may also increase risk of hypotension; for further guidance on the continued use of these concomitant medications in patients treated with bempegaldesleukin, please consult the Medical Monitor.

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

In 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.

5.14 Adverse Events

All AEs, either reported by the patient or observed by study staff, will be recorded 100 (± 7) days after the last dose of all study treatment(s) (Safety Follow-up Visit 2) (Table 4, Section 8.5). This study will use the Medical Dictionary for Regulatory Activities for coding all AEs. AEs will be summarized by preferred term, system organ class, grade of severity, and relationship to each study drug (bempegaldesleukin and/or nivolumab).

5.15 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 IRT will be employed to manage patient randomization and drug supply.

6.0 INVESTIGATIONAL PRODUCTS/STUDY DRUGS

6.1 Bempegaldesleukin (NKTR-214)

6.1.1 Drug Description and Formulation

[redacted]

[redacted]

6.1.2 Drug Packaging and Labeling

[redacted]

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

6.1.3 Drug Reconstitution and Handling

Instructions for reconstitution and handling of bempegaldesleukin (NKTR-214) drug product are provided in the Pharmacy Manual.

6.1.4 Drug Storage

Bempegaldesleukin drug product should be stored in a secure, locked area within temperature range, as specified on the drug label and Table 7.

6.1.5 Drug Shipment

For all countries, Nektar will supply bempegaldesleukin and nivolumab from a central source. Refer to the Pharmacy Manual for additional details.

6.2 Nivolumab Preparation, Storage, and Packaging

Refer to the Pharmacy Manual for details.

6.3 Study Drug Accountability and Reconciliation

Bempegaldesleukin and nivolumab are considered Investigational Medical Products and will be supplied to the Investigator by Nektar Therapeutics or its designee. Depending on source of supply, the packaging and labeling will vary. Products will be labeled to meet local country requirements. Please refer to the Pharmacy Manual for details.

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 dispensation such as:

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

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

7.0 ASSESSMENT OF EFFICACY

7.1 Imaging Assessments for the Study

Images will be submitted to an imaging core laboratory on an ongoing basis until BICR-confirmed distant recurrence. Sites should be qualified prior to scanning the first patient and understand the image acquisition guidelines and submission process as outlined in the Study 20-214-29/CA045-022 Imaging Manual provided by the imaging core laboratory.

Screening and follow-up images should be acquired as outlined in Section 1.2 (Schedule of Events). Radiographic tumor assessments will continue to be collected every 12 weeks (± 7 days) for up to 24 months from the date of randomization and then every 6 months (± 4 weeks) for up to 5 years (60 months) from the date of randomization until investigator-assessed and BICR-confirmed distant recurrence.

- For non-radiological recurrence, results of the biopsy confirming recurrence will be sent to the imaging core laboratory.
- For radiologic recurrence confirmed by biopsy, results will also be sent to the imaging core laboratory.

Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the imaging core laboratory as soon as possible. If a patient starts systemic therapy for a new non-melanoma tumor after study drug discontinuation, follow-up scans can be done as per standard of care. Unscheduled imaging (CT/MRI, bone scan, and/or positron emission tomography [PET] scan) should be submitted to imaging core laboratory. An ultrasound of the sentinel-node basin and fluorodeoxyglucose (FDG)-PET should be submitted to the imaging core laboratory if recurrence was initially detected using either method and confirmed at a later time.

Clinical data, including stage information and primary site of disease, will also be submitted to the imaging core laboratory (e.g., details regarding surgery, biopsy, and procedures).

7.2 Definitions

Recurrence:

Recurrence is defined as the appearance of one or more new melanoma lesions, which can be local, regional, or distant in location from the primary resected site, based on modified criteria from RECIST version 1.1 (Eisenhauer, 2009):

- The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor). If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If subsequent or repeat scans confirm there is definitely a new lesion, then recurrence should be declared using the date of the initial scan.

- If new lesions are identified by ultrasound in the course of the study, confirmation by biopsy or by CT or MRI should be performed and the results shared with the BICR (if so, the date of recurrence will be the date of the initial ultrasound). Suspected new pathological lymph nodes must be either ≥ 10 mm the short axis on CT or MRI or confirmed as recurrent disease by biopsy.
- FDG-PET scanning may be used to complement CT scanning in assessment of possible recurrence. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT or MRI, this is disease recurrence. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT or MRI, additional follow-up CT or MRI scans are needed to determine if there is truly progression occurring at that site (if so, the date of recurrence will be the date of the initial abnormal FDG-PET scan and the results shared with the BICR). A biopsy to confirm recurrence is strongly advised if safe to do so for recurrences initially identified by FDG-PET.

Local Recurrence:

Local cutaneous recurrence after adequate excision of the primary melanoma is associated with aggressive tumor biologic features and is frequently a harbinger of metastases. It is generally accepted that local recurrences occur within 2 cm of the tumor bed.

Regional Recurrence:

The neoplastic nature of the regional recurrences should be confirmed by histology/cytology.

- In-Transit Metastases: The AJCC defines in-transit metastases as any skin or subcutaneous metastases that are > 2 cm from the primary lesion but are not beyond the regional nodal basin. In-transit metastases occur in 10% to 15% of patients with Stage III disease. When present, in-transit metastases are usually multiple, evolve over time, and are often the harbinger of subsequent systemic disease.
- Regional Node Recurrences: Regional node failure in a previously dissected basin is usually found at the periphery of the prior surgical procedure.

Distant Recurrence:

Melanoma is well known for its ability to metastasize to virtually any organ or tissue. The most common initial sites of distance metastases are the non-visceral (skin, subcutaneous tissue, and lymph nodes), which are recurrence sites for 42% to 59% of subjects in various studies. Visceral locations are the lung, brain, liver, gastrointestinal tract, and bone; the visceral sites are the initial sites of relapse in approximately 25% of all melanoma patients who experience recurrence.

Distant metastases may be measurable or non-measurable.

Note:

- Cutaneous relapses occurring beyond the periphery of the previous surgical bed (i.e., > 2 cm) are considered distant metastases.
- Node relapses occurring beyond the anatomical compartment of the dissected basins are considered distant metastases.
- Node relapses in nodal basins situated in a different anatomical compartment or beyond the previously dissected basin or in two nodal basins (even if contiguous; i.e., 2 pelvic nodal basins, 2 mediastinal nodal basins) are considered distant metastases.

Date of Recurrence:

The first date when recurrence was observed is taken into account regardless the method of assessment. Therefore, recurrence will be declared for any lesion when:

- Only imaging was performed and recurrence confirmed
- Only pathology was done and malignancy confirmed (in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions)
- Both pathology and imaging were done and recurrence/malignancy confirmed. In this case, the date of whichever examination comes first is considered the date of recurrence.

Results of biopsies confirming recurrence should be sent to the imaging core laboratory.

Note: for documentation, the date of recurrence is the date that the pathology and/or imaging confirms recurrence--not the date that the information was communicated to the patient.

7.3 Methods of Imaging

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

Contrast-enhanced CT of the chest; contrast-enhanced CT or MRI of the abdomen and pelvis; and all known sites of resected disease should be performed for tumor assessments. Images should be acquired with slice thickness of ≤ 5 mm with no intervening gap (contiguous). Every attempt should be made to image each patient using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same Investigator or radiologist for each assessment whenever possible.

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

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

Should a patient have contraindication for MRI (e.g., incompatible pacemaker) in addition to contraindication to CT intravenous contrast, a non-contrast CT of the chest, abdomen, pelvis, and all known sites of resected disease is acceptable after discussion and agreement with the Medical Monitor.

PET alone will not be considered for the disease assessment. Complementary CT and/or MRI and/or biopsy must be performed in such cases. Use of CT component of a PET-CT scanner: If a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used to determine recurrence.

Brain imaging for patients with baseline history of treated brain lesions: Brain MRI required at baseline (without and with contrast; head CT with contrast allowed on study if patient develops contraindication for MRI). Brain imaging for patients without baseline history of brain metastases: Brain MRI (without and with contrast; head CT with contrast allowed if MRI contraindicated).

Ultrasound of sentinel-node basin as surveillance imaging is required.

Histological or cytological evidence of recurrence should be attempted in all cases except for brain metastases when safe and clinically feasible.

For clinically detected new lesions:

- Superficial cutaneous lesions: the recurrence of melanoma must be confirmed by cytology/histology.
- Deep subcutaneous lesions and lymph node lesions should be documented by ultrasound and histological/cytological evidence should be attempted. In absence of pathology report, lesion recurrence will be documented with a CT scan/MRI.
- Tumor markers or auto-antibodies alone cannot be used to assess recurrence.

7.4 Patient-Reported Outcomes

Health-related quality of life (HRQoL) will be assessed at the time points stipulated in the Schedule of Events (Section 1.2) by EORTC QLQ-C30 and EQ-5D-5L in patients who are ≥ 18 years of age at the time of informed consent. The EORTC QLQ-C30 and EQ-5D-5L should be assessed before any other study-related procedures are performed, with the EORTC QLQ-C30 assessed before the EQ-5D-5L. Paper forms should be used when patients are in the clinic and phone script should be used when patients are in follow-up.

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

The questionnaire will be completed by the subjects before any clinical assessments are performed and treatments administered at any given visit. If subjects 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 subject, and subjects should be given adequate time and space to complete the questionnaire.

7.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 will be used as a measure of HRQoL. The EORTC QLQ-C30 is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/HRQoL scale, and six 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-C30 employs a week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories of "Not at all", "A little", "Quite a bit" and "Very much". The two items assessing global health status/HRQoL utilize a 7-point scale ranging from 1 ("Very Poor") to 7 ("Excellent") (Aaronson, 1993).

For the purpose of this study, the GH/QoL and physical functioning subscales were selected as secondary endpoints. These subscales were selected as most commonly used indicators of HRQoL across cancer indications. [redacted]

7.4.2 EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (Herdman, 2011; EuroQol, 1990; Aaronson, 1993). The EQ-5D-5L has 2 components: a descriptive system and a visual analogue scale. The EQ-5D-5L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels including "no," "slight," "moderate," "severe," and "extreme" or "unable to." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Accordingly, the vectors 11111 and 55555 represent the best health state and the worst health state, respectively, described by the EQ-5D-5L. Altogether, the instrument describes $5^5 = 3{,}125$ health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate a utility index measuring the value to society of his or her current health. In addition,

the EQ-5D-5L visual analogue scale allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health. Thresholds for meaningful change for the EQ-5D-5L utility index and visual analogue scale in cancer patients have not been defined. The EQ-5D-5L is available in more than 130 languages.

A standardized script will be used to facilitate telephone administration of the EQ-5D-5L during Survival Follow-up Visits.

8.0 ASSESSMENT OF SAFETY

8.1 AE Definition and Assessment

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

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can also arise from any use of the drug and from any route of administration, formulation, dose, or overdose. This definition includes intercurrent illnesses or injuries, and exacerbation of pre-existing conditions. Clinical laboratory, vital sign, or physical examination abnormalities will only be reported as AEs if they are deemed clinically significant by the Investigator (e.g., associated with signs and symptoms, require treatment, or require follow-up). The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

An AE does not include:

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

8.2 Monitoring AEs

All AEs will be assessed by the Investigator and recorded, including but not limited to, the following: the event term, the date of onset and resolution, seriousness, severity, relationship to study drug(s), outcome, treatment of the event, and action taken with the study drug(s). AEs will be reported starting immediately after the patient has been administered the first dose of study drug(s) until 100 (± 7) days following the last dose of study treatment(s) (Safety Follow-up Visit 2). For treatment-related SAEs, additional reporting requirements also apply (see Section 8.7).

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

condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Under the latter 2 circumstances, the event will be considered an AE and will be captured as such.

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

8.3 Grading of AEs

The severity of an event and the seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of event is based on the patient/event outcome or action criteria. All AEs will be assessed for severity using the National Cancer Institute 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 [e.g., insomnia, mild headache]).
- Grade 2 = Moderate (event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment [e.g., fever requiring antipyretic medication]).
- Grade 3 = Severe (event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention).
- Grade 4 = Life-threatening or disabling.
- Grade 5 = Death.

Severity for all AEs will be recorded according to the highest severity grade a patient experiences for the duration of that AE.

8.4 Causality Relationship of AEs

The relationship of each AE to each study drug (bempegaldesleukin and/or nivolumab) as applicable will be evaluated by the Investigator using the following definitions:

- Not related: An AE that does not follow a reasonable temporal sequence from administration of study drug(s), and/or that can be reasonably explained by other factors such as the patient's pre-existing medical condition, underlying disease, concurrent illness, or concomitant medications/therapies.

- Related: There is a reasonable possibility that 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.

8.5 AE Reporting and Follow-up

After initiation of study drug treatment, all AEs except for SAEs (Section 8.7 and 8.8) will be reported from the time of first study drug(s) administration until 100 (± 7) days after the last dose of all study treatment(s) (Safety Follow-up Visit 2) (see Section 5.5).

All ongoing nonserious AEs will be followed until resolution, the patient is lost to follow-up, patient death, or until the Safety Follow-up Visit 2 (or 100 [± 7] days after the last dose of study treatment). If the AE has not completely resolved by the last Safety Follow-up Visit, the final outcome of these ongoing AEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

For specific instructions on identifying and reporting SAEs, see Sections 8.6 and 8.7.

8.6 Serious AE Definition

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

- Results in death.
- Is life-threatening, i.e., in the opinion of the Investigator, the AE places the patient at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization (for ≥ 24 hours) that occurs during the course of a patient's participation in a clinical study, except for those due to the following:
  - A surgery or procedure that was planned before the patient entered the study and which is part of the planned study procedure.
  - Nonmedical reasons, in the absence of an AE (e.g., admit for overnight observation after the first dose of study drug, per Investigator judgment).
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed above.

Death is an outcome of an AE and not an AE in itself. All events leading to death, regardless of relationship to study drugs, that occur during the protocol-specified reporting period, must be

reported with the exception of deaths attributed to disease progression (refer to Section 8.9). An efficacy failure is not considered an SAE. "Life-threatening" means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity. "Inpatient hospitalization" means the patient has been admitted to a hospital for medical reasons for any length of time. Additionally, if the patient presents and remains in the Emergency Room for more than 24 hours, the event will have met the inpatient hospitalization criteria. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

8.7 Serious AE Reporting

Serious AEs occurring after the patient has provided informed consent, but before the first dose of study treatment or confirmed screen failure, will be collected as medical history unless the event is either new and attributed to protocol-mandated procedures by the Investigator or there is a significant change in the rate of occurrence or an increase in the severity of the pre-existing condition which is judged to be clinically important and attributed to the protocol-mandated procedures by the Investigator. Any new or clinically significant changes in the patient's medical and/or cancer history that occur after the first dose of drug and meet the SAE criteria will be recorded as SAEs. All SAEs, regardless of causality or starting subsequent anticancer therapy, with an onset within 100 (± 7) days after the last dose of all study treatment(s) will be reported to Nektar Therapeutics Drug Safety immediately (i.e., no more than 24 hours after learning of the event).

In addition, all SAEs that occur beyond 100 (± 7) days after last dose of all study treatment(s) that are assessed by the Investigator as related to study drug(s) will also be reported to Nektar Therapeutics Drug Safety within 24 hours of awareness of the event.

All AEs and SAEs will be recorded in the electronic case report form (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, i.e., the eCRF database is not functioning, record the SAE on the paper SAE reporting form and submit within 24 hours of the

Investigator's knowledge of the event to Nektar Therapeutics Drug Safety via email or Safety Fax as listed at the beginning of this protocol.

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

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

All SAEs will be followed as described in Section 8.8.

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

8.8 Serious AE Follow-up

All study treatment-related SAEs that have not resolved by the Safety Follow-up Visit 2 (or 100 [± 7] days after the last dose of study treatment) (Section 5.5) will be followed until any of the following occur (whichever comes first):

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

All SAEs assessed as unrelated to study drug(s) will be followed until resolution or until the last Safety Follow-up Visit (Section 5.5), whichever is earlier. In the case where an unrelated SAE has not completely resolved by the Safety Follow-up Visit 2 (or 100 [± 7]) days after the last dose of study treatment), the final outcome of these ongoing unrelated SAEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving", whichever is applicable.

8.9 Disease Recurrence and Death due to Disease Recurrence – 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, e.g., 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.

8.10 Adverse Events of Special Interest

The AE listed below is considered an AESI. Regardless of the assessment of whether the AESI is serious or nonserious, all AESIs are required to follow the timeline for SAE reporting (within 24 hours as described in Section 8.7) from the sites to Nektar Drug Safety: pharmacovigilance@nektar.com.

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

8.11 Immune-mediated Adverse Events and Other Monitored Events

Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. 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.

Additional information may also be collected on immune-mediated adverse events.

8.12 Additional Information Collected for Adverse Events Primarily Related to Bempegaldesleukin

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

8.13 Pregnancy Tests/Pregnancy

8.13.1 Pregnancy Tests

Serum or urine pregnancy tests will be performed on WOCBP during according to the Schedule of Events (Section 1.2). Urine pregnancy tests should have a minimum sensitivity of 25 IU/L or equivalent units of HCG. A negative pregnancy test result must be obtained within 24 hours before the administration of the study drug(s).

A pregnancy test does not need to be performed on women who are postmenopausal (see Appendix 4).

8.13.2 Pregnancy

8.13.2.1 Pregnancies in Female Patients

The Sponsor must be notified immediately without undue delay, under no circumstances later than 24 hours following knowledge of the initial report and any follow-up reports of a female patient becoming pregnant during the course of the study and for 5 months after the last dose of nivolumab. All reports should be submitted via the Pregnancy Notification Form. Pregnancy, although reportable, is not considered an AE/SAE unless a female patient experiences signs or symptoms of pregnancy complications; however, the contact information for pregnancy reporting is the same as for SAE reporting and listed in Section 8.7. Female patient(s) who become pregnant will be followed until the outcome of the pregnancy is known. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring.

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

If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed at the discretion of the Investigator (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended) following approvals of the patient and IRB/IEC, as applicable.

8.13.2.2 Pregnancies in Female Partners of Male Patients

Any pregnancy occurring up to 7 months after the last dose of nivolumab 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 ICF (see Section 12.2).

Pregnancy, although reportable, is not considered an AE/SAE unless a female partner of male patient experiences signs or symptoms of pregnancy complications; however, the contact information for pregnancy reporting is the same as for SAE reporting and listed in Section 8.7. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug with the authorization from the pregnant partner. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring.

8.14 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 8.7 for reporting details).

Potential DILI is defined as:

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

AND

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

AND

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

8.15 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 healthcare 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.

8.16 Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Events (Section 1.2). Clinical laboratory tests for Screening, prior to Day 1 of each cycle thereafter and for Safety Follow-Up Visits will be performed by the central and local laboratories. For eligibility review, if central laboratory tests are cancelled, lost, considered inadequate for analysis, or cannot be processed, local laboratory results provided by the site may be used to determine eligibility. A list of the clinical laboratory analytes to be tested is provided in Appendix 1. Additional clinical laboratory tests may be ordered at the Investigator's or Sub-Investigator's discretion.

Clinical laboratory test data will be reviewed by the Investigator or Sub-Investigator for clinical significance and to make treatment decisions. Any laboratory result deemed clinically significant (i.e., is associated with signs and symptoms, requires treatment, or requires follow-up) will be recorded as an AE as described in Section 8.1.

8.17 Physical Examinations

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

8.18 Vital Signs and Oxygen Saturation

Vital sign measurements will be recorded according to the Schedule of Events (Section 1.2). Vital signs include pulse rate, systolic and diastolic blood pressure, respiratory rate, and

temperature at all time points, as well as pulse oximetry at Screening only. 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.

8.19 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. After randomization, ECGs will be performed if clinically indicated.

8.20 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.

9.0 STATISTICAL PLAN

9.1 General Considerations

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

All efficacy endpoints will be analyzed using the ITT population. All safety endpoints will be summarized using the safety population.

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

9.2 Determination of Sample Size

Up to 950 Stage III/IV melanoma patients at high risk of recurrence will be randomized into the two arms (bempegaldesleukin plus nivolumab vs. nivolumab) in a 1:1 ratio. Enrollment of 950 patients is estimated to take approximately 22.5 months, assuming an enrollment rate of 50 patients/month, with a 7-month of ramp-up.

The sample size is calculated to power the comparison of RFS between the two treatment arms in the ITT population. Based on the RFS results for nivolumab from Bristol-Meyers Squibb study CheckMate-238, a non-constant RFS hazard was observed. Thus, for sample size calculation, a piecewise exponential distribution was assumed in each treatment arm with a constant hazard ratio of 0.7. Specifically, in the nivolumab arm, four different hazard rates were assumed before 3 months, between 3 and 12 months, between 12 and 24 months, and after 24 months, corresponding to RFS rates of 90%, 70.5%, 62%, and 51.7% at 3, 12, 24, and 48 months, respectively. At a two-sided overall alpha level of 0.05, a total of 400 RFS events are needed to detect a hazard ratio of 0.7 with 94% power. The final analysis will occur if 400 events are observed or a minimum follow-up of 45 months is reached, whichever occurs first. Given an enrollment period of 22.5 months, minimum follow-up of 45 months, and a 5% annual dropout rate, a total sample size of 950 patients (475 per treatment arm) is required to observe the needed 400 RFS events at 68 months from first patient first visit (FPFV) for final analysis. It is projected that an observed hazard ratio of 0.811 or less would result in a statistically significant improvement in the final analysis of RFS.

Two formal interim analyses of RFS are planned for this study (Table 12). The first interim analysis will be performed when approximately 320 events (80% of the targeted RFS events for final analysis) are observed, which is expected to be 42 months from FPFV. The second interim analysis will be performed when approximately 360 events (90% of the targeted RFS events for final analysis) are observed, which is expected to be 54 months from FPFV. The stopping boundaries at interim and final analyses will be derived based on the actual number of observed

events using O'Brien and Fleming alpha spending function in software EAST 6.4.1. If the number of events are exactly as planned, the critical p-value boundaries (two-sided) at each planned analysis for 320 RFS events at 42 months from FPFV, for 360 events at 54 months from FPFV (2 interim analyses), and the final analysis (400 events) at 68 months from FPFV are 0.0244 (interim 1), 0.0295 (interim 2), and 0.0383 (final), respectively. The corresponding critical boundaries on hazard ratios are 0.776 (interim 1), 0.793 (interim 2) and 0.811 (final analysis), respectively.

The secondary endpoint of OS will be tested hierarchically given the significance of RFS.

Table 12: Formal Interim Analyses for RFS

Analyses	No. of Events	Time (Month) from FPFV	Critical P-value (2-sided)	Critical HR
1st interim analysis	320	42	0.0244	0.776
2nd interim analysis	360	54	0.0295	0.793
Final analysis	400	68	0.0383	0.811

FPFV = first patient first visit; HR = hazard ratio; No. = number; RFS = recurrence-free survival.

9.3 Analysis Sets

For the purposes of analysis, the following populations are defined in Table 13.

Table 13: Analysis Populations

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.
Safety Population	All patients who receive at least 1 dose (or partial dose) of study drug. Patients are grouped according to the treatment they actually received. 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 treated patients with baseline and at least 1 post-baseline immunogenicity assessment.
Biomarker Population	All randomized patients who have biomarker data available at baseline. For pharmacodynamic biomarkers, the biomarker population includes all randomized patients who have baseline and at least one post-baseline biomarker data available.
HRQoL Population	All patients in the ITT population who had a baseline and at least 1 post-baseline assessment (defined for each instrument).

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

9.4 Endpoints

9.4.1 Primary Endpoint

The primary endpoint is RFS by BICR, which will be programmatically determined based on the disease recurrence date provided by BICR and is defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis by BICR), new primary melanoma (by BICR), or all-cause death, whichever occurs first. (Note: a patient who dies without reported recurrence will be considered to have recurred on the date of death.) For patients who remain alive and whose disease has not recurred, RFS will be censored on the date of last evaluable disease assessment. For those patients who remained alive and had no recorded post-randomization tumor assessment, RFS will be censored on the day of randomization. Censoring rules for the primary analysis of RFS are presented in Table 14.

Table 14: Censoring Scheme for Primary Definition of RFS

Situation	Date of Event or Censoring	Outcome
Recurrence (local, regional, distant, new primary melanoma)	Date of first recurrence	Event
Death without recurrence	Date of death	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored
New anticancer therapy (for melanoma or second non-melanoma primary cancer), including melanoma tumor-directed radiotherapy and melanoma tumor-directed surgery, received without recurrence reported prior to or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored

9.4.2 Secondary Endpoints

Secondary endpoints are presented in Table 15.

Table 15: Secondary Endpoints

Endpoint	Description
OS	Defined as the time between the date of randomization and the date of death due to any cause. Patients who do not have a date of death will be censored on the last date for which a patient was known to be alive. Evaluated in the ITT population.
DMFS by BICR	Defined as the time between the date of randomization and the date of first distant metastasis by BICR or date of death due to any cause, whichever occurs first. For patients who remain alive and distant metastasis-free, DMFS will be censored on the date of last disease assessment. DMFS will be evaluated in patients who are Stage III at study entry.
DMFS by Investigator	Defined as the time between the date of randomization and the date of first distant metastasis by Investigator or date of death due to any cause, whichever occurs first. For patients who remain alive and distant metastasis-free, DMFS will be censored on the date of last disease assessment. DMFS will be evaluated in patients who are Stage III at study entry.
PFS2	PFS2 is defined as time from randomization to progression per Investigator after the start of next line of therapy or death, whichever occurs first. Patients who were alive and without progression after the next line of therapy can be censored at last known alive date. Evaluated in the ITT population. Details on the PFS2 analysis will be described in the SAP.
Overall Safety and Tolerability	Measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities in the safety population.

Table 15: Secondary Endpoints (Cont'd)

Endpoint	Description
PROs	Measured by (group-level and individual-level) changes from baseline in scores for the GH/QoL and physical functioning subscales of the EORTC QLQ-C30 questionnaire.
PD-L1 Expression as a Predictive Biomarker for RFS	Measured by the RFS by BICR endpoints based on PD-L1 expression level.
RFS by Investigator	Defined similar to the primary endpoint, but recurrence and new primary melanoma are decided by Investigator.

BICR = blinded independent central review; DMFS = distant metastasis-free survival; EORTC QLQ-C30 = 30-item European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; GH/QoL = global health/quality of life; ITT = intent-to-treat; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS2 = progression-free survival after next line of treatment; PROs = patient-reported outcomes; RFS = recurrence-free survival; SAP = statistical analysis plan.

[redacted]

9.5 Demographics and Baseline Characteristics

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

9.6 Efficacy Analyses

9.6.1 Primary Analyses

A log-rank test stratified by Stage and PD-L1 status will be used to compare RFS between the two treatment arms in the ITT population at an overall alpha level of 0.05 (two-sided). A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the hazard ratio and corresponding 95% CI. The Kaplan-Meier method will be used to further summarize RFS, including Kaplan-Meier curves, medians with corresponding 95% CIs, and RFS rates at 6, 12, 18, 24, and every 12 months thereafter with 95% CIs.

Details and additional sensitivity analyses will be described in the SAP.

9.6.2 Secondary Analyses

Only RFS by BICR and OS are formally tested with an overall type I error controlled at 0.05 level via closed sequential testing procedure. If RFS by BICR is statistically significant at any of the planned analyses, the OS endpoint will be tested at 0.05 alpha level when the follow-up time is at least 5 years for all patients.

The secondary analysis of OS in the ITT population will be conducted using a two-sided log-rank test stratified by randomization stratification factors only if the primary analysis of RFS claims significance. A stratified Cox proportional hazards model with treatment as the single covariate will be used to estimate the hazard ratio and corresponding 95% CI. The Kaplan-Meier method will be used to further summarize OS, including Kaplan-Meier curves, medians with corresponding 95% CIs, and OS rates at 6, 12, 18, 24, and every 12 months thereafter with 95% CIs.

To calculate power for the OS comparison, a piecewise exponential distribution can be assumed in each treatment arm with a constant hazard ratio of 0.75. Specifically, in the nivolumab arm, three different hazard rates are assumed before 3 months, between 3 and 36 months, and after 36 months, corresponding to OS rates of 99%, 75%, and 65% at 3, 36, and 60 months, respectively.

The OS endpoint will be tested at a two-sided alpha level of 0.05 only if RFS by BICR is statistically significant at any of the planned analyses and when all patients have the minimum 5-year follow-up, regardless of the number of OS events observed by then. This OS analysis is projected to occur at 83 months from the first patient randomized (~23 months of accrual and 60 months of follow-up based on current enrollment assumptions). Approximately 330 OS events are expected to be observed by then, which will provide 74% power to detect a hazard

ratio of 0.75. The critical hazard ratio is 0.806 if exactly 330 OS events are observed at the time of analysis. The standard Kaplan-Meier estimate and Cox regression model will be used to analyze the OS endpoint.

Under the current enrollment assumptions, it is expected that 177, 229, and 277 OS events will be observed at the first and second interim and the final RFS analysis at 42 months, 54 months, and 68 months from the first patient randomized, respectively.

Other secondary [redacted] endpoints will be analyzed similarly to OS. Details of these secondary analyses will be described in the SAP.

To evaluate PD-L1 expression as a predictive biomarker, a Cox proportional hazards model will be used to test the interaction between PD-L1 expression (≥ 1% vs < 1%) and treatment arm for the RFS endpoints. Additionally, RFS will be analyzed within each PD-L1 expression subgroup (≥ 1% vs < 1%) including log-rank tests and hazard ratios with corresponding CIs. The Kaplan-Meier method will be used to further summarize RFS, including Kaplan-Meier curves, medians and 95% CIs, and RFS rates in each subgroup at 6, 12, 18, 24, and every 12 months thereafter with 95% CIs. The analyses will be descriptive.

The analysis of EORTC QLQ-C30 data will be performed in the HRQoL population (defined in Section 9.3). Scores for all EORTC QLQ-C30 items and subscales will be linearly transformed to a 0 to 100 metric where higher values indicate better functioning/well-being or lower symptom burden (see EORTC QLQ-C30 Scoring Manual). The primary domains of interest for the HRQoL analysis are GH/QoL and physical functioning of EORTC QLQ-C30.

Scores and post-baseline mean score changes and percent of subjects' HRQoL response status (e.g., improved, worsened, no change) compared to their baseline for the EORTC QLQ-C30 primary subscales will be summarized (e.g., mean with standard deviation and 95% CI, median, minimum, maximum) by treatment group and assessment time point. The clinically meaningful change for group-level analysis will be defined for each EORTC QLQ-30 domain as recommended by the literature (Musoro, 2018), specifically as 7 for GH/QoL and 5 for physical functioning. For individual-level analysis (i.e., percent of subjects who achieved the HRQoL change), the clinically meaningful change thresholds will be defined as 5 (-5) for improvement (deterioration) for both GH/QoL and physical functioning (Cocks, 2015).

[redacted]

9.7 Safety Analyses

Safety analyses will be performed in all treated patients. Descriptive statistics of safety will be presented using NCI-CTCAE version 5.0 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI-CTCAE version 5.0 criteria by system organ class and preferred term. On study lab

parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI-CTCAE version 5.0 criteria.

9.8 Interim and Final Analyses

- Interim Analysis 1 (IA1): when approximately 320 RFS events have been observed.
- Interim Analysis 2 (IA2): when approximately 360 RFS events have been observed.
- Final Analysis: when approximately 400 RFS events have been observed or a minimum follow-up of 44 months has been reached, whichever occurs first.

[redacted]

9.9.1 Pharmacokinetic Analyses

Plasma concentrations of bempegaldesleukin-related molecules and serum concentrations of nivolumab will be measured using validated or qualified method(s). Pharmacokinetic endpoint analyses are presented in Table 17.

Table 17: Pharmacokinetic Analyses

Endpoint	Statistical Analysis Methods
C_{max}	Summary statistics: geometric means and coefficients of variation
T_{max}	Summary statistics: medians and ranges

C_{max} = maximum observed concentration; T_{max} = time to maximum observed concentration.

A noncompartmental analysis approach will be used to estimate C_{max} and time to maximum observed plasma concentration (T_{max}). PPK approaches will be used to estimate the AUC, clearance (CL), and volume of distribution (V_d). Model predicted exposures may be used for exposure-response analyses of selected efficacy and safety endpoints. If the analyses are conducted, the results of PPK and exposure-response analyses will be reported separately.

9.9.2 Immunogenicity Analyses

Immunogenicity will be reported for ADA positive status for anti-nivolumab/anti-bempegaldesleukin/anti-PEG (such as persistent positive, other positive, only last sample positive, baseline positive) and ADA negative status, relative to baseline. In addition, presence of neutralizing antibody may be reported, if applicable. Effect of immunogenicity on safety/efficacy and PK may be explored.

9.10 Independent Data Monitoring Committee

An IDMC will be established to provide oversight of safety and efficacy considerations in the protocol and to provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of patients enrolled in the study. The IDMC will be charged with assessing such actions in light of an acceptable benefit-risk profile for bempegaldesleukin and nivolumab. The IDMC will act in an advisory capacity to Sponsor and will monitor patient safety and evaluate the available efficacy data for the study. The Sponsor has primary responsibility for design and conduct of the study.

The IDMC will be comprised of qualified clinicians and a biostatistician, all independent from the Sponsor and investigational sites, selected to avoid conflict(s) of interest. The IDMC'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 IDMC recommendations, and regulatory reporting, as applicable. The charter will contain procedures to ensure the minimization of bias, such as maintaining confidentiality of any interim data.

10.0 STUDY OR STUDY SITE TERMINATION

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

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

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

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

11.1 Changes to the Protocol

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/IEC and 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 non-evaluable. All protocol deviations and the reasons for such deviations are to be documented and reported to the Sponsor.

11.2 Monitoring

In accordance with Code of Federal Regulations 21 CFR 312.56, International Council for Harmonisation (ICH) GCP, and local regulations, the clinical monitor will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR 312 Subpart D (Responsibilities of Sponsors and Investigators), ICH GCP, and local regulations, the monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs; ensure that all protocol requirements, applicable FDA, ICH GCP, and local regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) for the patients in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor. The Investigational New Drug Application (IND) regulations and ICH E6 guidelines also require the Investigator to allow authorized representatives of the Sponsor, IRB/IEC, FDA, and other relevant Regulatory Authorities direct access to study source records, and to inspect and make copies of the same records. The names and identities of the patients need not be divulged to the Sponsor; however, the records must nevertheless be available to be inspected for review. This can be accomplished by blacking out the patient's name and replacing the name with the patient's study identification number. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the Investigator must inform the Sponsor of these restrictions before initiation of the study.

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

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

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

12.0 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.

12.1 IRB/IEC Approval

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

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

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

12.2 Written Informed Consent

Written documentation of informed consent must be obtained from each patient or (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 ICF for disclosure information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

13.0 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection Instruments and Source Documents

13.1.1 Study Records

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

13.1.2 Data Collection Instruments

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

13.2 Retention of Essential Documents

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

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

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

13.3 Confidentiality

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

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 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 a patient’s personal data.

13.4 Security Measures

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

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

14.0 PUBLICATION PLAN

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

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

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

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APPENDIX 1: 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: Local Clinical Laboratory Tests Obtained Prior to Bempegaldesleukin and/or Nivolumab Study Drug Administration

Appendix 1A: Laboratory Tests Performed in This Study

<table>
<tr><th colspan="3">Clinical Laboratory Tests[a]</th></tr>
<tr><th>Hematology</th><th>Chemistry</th><th>Serology (Screening Only)</th></tr>
<tr><td rowspan="4">• Hemoglobin (Hgb)
• Hematocrit (HCT)
• Platelet count
• White blood cell (WBC) count
• Neutrophil count
• Lymphocyte count
• Monocytes
• Eosinophil count
• Basophils</td><td rowspan="4">• AST (SGOT)
• ALT (SGPT)
• Alkaline phosphatase (ALP)
• Albumin
• Creatinine
• Calculated creatinine clearance
• Calcium
• Glucose
• Total protein (TP)
• Total bilirubin
• Sodium
• Potassium
• Chloride
• CO_2 content or bicarbonate
• Blood urea nitrogen (BUN) or serum urea
• Lactate dehydrogenase (LDH)
• Uric acid</td><td>• Hepatitis B surface antigen (HBsAg)
• Hepatitis C virus antibody (anti-HCV)
• Human immunodeficiency virus (HIV) antibody</td></tr>
<tr><td>Additional Labs</td></tr>
<tr><td>• Creatine kinase
• Thyroid-stimulating hormone (TSH)
• Free thyroxine (T4)
• Free or total triiodothyronine (T3)
• Lipase
• Amylase
• Serum or urine pregnancy</td></tr>
<tr><td>Coagulation[b]</td></tr>
<tr><td></td><td></td><td>• Partial thromboplastin time (PTT)
• Prothrombin time (PT)</td></tr>
<tr><td colspan="3">Urinalysis (Local Laboratory)
Performed at Screening and as clinically indicated.</td></tr>
<tr><td>• Appearance
• Bilirubin
• Blood
• Color
• Glucose
• Ketones
• Leukocyte esterase
• Nitrites
• pH
• Protein
• Specific gravity
• Urobilinogen</td><td colspan="2">For positive protein, white blood cell, or blood, a microscopic examination including:
• Red blood cells
• White blood cells
• Epithelial cells
• Bacteria
• Crystals
• Casts
• Parasites
• Yeast</td></tr>
</table>

a. Clinical laboratory tests are to be collected at each time point specified in Section 1.2. Performed by central laboratory. For eligibility review, if central laboratory tests are cancelled, lost, considered inadequate for analysis, or cannot be processed, local laboratory results provided by the site may be used to determine eligibility.

b. Coagulation is not required at Screening.

Appendix 1B: Local Clinical Laboratory Tests Obtained Prior to Bempegaldesleukin and/or Nivolumab Study Drug Administration

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

WOCBP = women of childbearing potential.

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

APPENDIX 2: AMERICAN JOINT COMMITTEE ON CANCER DEFINITIONS FOR T, N, M STAGING AND PROGNOSTIC STAGE GROUPS

Definition of Primary Tumor (T)[a]

T Category	Thickness	Ulceration Status
TX: Primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma in situ)	Not applicable	Not applicable
T1	≤ 1.0 mm	Unknown or unspecified
T1a	< 0.8 mm	Without ulceration
T1b	< 0.8 mm	With ulceration
	0.8–1.0 mm	With or without ulceration
T2	> 1.0–2.0 mm	Unknown or unspecified
T2a	> 1.0–2.0 mm	Without ulceration
T2b	> 1.0–2.0 mm	With ulceration
T3	> 2.0–4.0 mm	Unknown or unspecified
T3a	> 2.0–4.0 mm	Without ulceration
T3b	> 2.0–4.0 mm	With ulceration
T4	> 4.0 mm	Unknown or unspecified
T4a	> 4.0 mm	Without ulceration
T4b	> 4.0 mm	With ulceration

AJCC = American Joint Committee on Cancer; T = tumor.

a. The original and primary source for this information is the AJCC Cancer Staging Manual, eighth edition (2017) published by Springer International Publishing (modified from: Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563–585).

Source: Gershenwald, 2017 (Table 2)

Definition of Regional Lymph Node (N)[a]

Extent of Regional Lymph Node and/or Lymphatic Metastasis		
N Category	**No. of Tumor-Involved Regional Lymph Nodes**	**Presence of In-Transit, Satellite, and/or Microsatellite Metastases**
NX	Regional nodes not assessed (e.g., sentinel lymph node [SLN] biopsy not performed, regional nodes previously removed for another reason); Exception: pathological N category is not required for T1 melanomas, use clinical N information	No
N0	No regional metastases detected	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or 3 tumor-involved nodes or any number of in-transit, satellite, and/or micro- satellite metastases with one tumor-involved node	
N2a	Two or 3 clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or 3, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

AJCC = American Joint Committee on Cancer; N = node.

a. The original and primary source for this information is the AJCC Cancer Staging Manual, eighth edition (2017) published by Springer International Publishing (modified from: Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563–585).

Source: Gershenwald, 2017 (Table 3)

Definition of Distant Metastasis (M)[a]

M Category[b]	M Criteria	
	Anatomic Site	**LDH Level**
M0	No evidence of distant metastasis	Not applicable
M1		
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

AJCC = American Joint Committee on Cancer; CNS = central nervous system; LDH = lactate dehydrogenase; M = metastasis.

a. The original and primary source for this information is the AJCC Cancer Staging Manual, eighth edition (2017) published by Springer International Publishing (Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563–585).

b. Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.

Source: Gershenwald, 2017 (Table 4)

AJCC Pathological (pTNM) Prognostic Stage Groups[a]

	T	N	M
Stage 0†	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1a/b, T2a	N1a, N2a	M0
Stage IIIB	T0	N1b, N1c	M0
	T1a/b, T2a	N1b/c, N2b	M0
	T2b, T3a	N1a/b/c, N2a/b	M0
Stage IIIC	T0	N2b/c, N3b/c	M0
	T1a/b, T2a/b, T3a	N2c, N3a/b/c	M0
	T3b, T4a	Any N ≥ N1	M0
	T4b	N1a/b/c, N2a/b/c	M0
Stage IIID	T4b	N3a/b/c	M0
Stage IV	Any T, Tis	Any N	M1

AJCC = American Joint Committee on Cancer; M = metastasis; N = node; T = tumor.

a. The original and primary source for this information is the AJCC Cancer Staging Manual, eighth edition (2017) published by Springer International Publishing (Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563–585).

† Pathological Stage 0 (melanoma in situ) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use clinical N information to assign pathological stage.

Source: Gershenwald, 2017 (Table 6)

APPENDIX 3: PERFORMANCE STATUS SCALES

PERFORMANCE STATUS CRITERIA: ECOG Score (≥ 17 years of age)	
Score	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.

Source: Oken, 1982

PERFORMANCE STATUS CRITERIA: Lansky (12 to 16 years of age, inclusive)	
Score	**Description**
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of, and less time spent, in active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

Source: Lansky, 1987

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

DEFINITIONS

Women of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PATIENTS OF CHILDBEARING POTENTIAL

At a minimum, patients must agree to use two effective methods of contraception, with one method being highly effective and another method from the list below during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment (Note: local laws and regulations may require use of alternative and/or additional contraception methods).

Highly Effective Contraceptive Methods That Are User <u>Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal Progestogen-only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly Effective Methods That Are User <u>Independent</u>
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Hormonal methods of contraception including vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS) • Intrauterine device (IUD) • Bilateral tubal occlusion • Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the 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 WOCBP patients choose to forego complete abstinence
Less Effective Methods of Contraception[b]
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

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

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the Investigator.
- Male patients are required to use a condom for study duration and until end of relevant systemic exposure defined as 3 months after the end of bempegaldesleukin treatment.
- Female partners of childbearing potential of males participating in the study to consider use of highly effective methods of contraception, listed in the table above, until the end of relevant systemic exposure, defined as 3 months after the end of bempegaldesleukin treatment 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 end of bempegaldesleukin treatment.
- Refrain from donating sperm for the duration of the study treatment and until 3 months after the end of bempegaldesleukin treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information is provided in Section 8.13.2.

APPENDIX 5: CORTICOSTEROID DOSE EQUIVALENTS

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

Mager, 2003; Webb, 2005

APPENDIX 6: CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM FOR THE COMBINATION OF BEMPEGALDESLEUKIN WITH CHECKPOINT INHIBITORS

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

For unexplained neurological symptoms (such as hemiparesis, confusion, dysarthria, or visual disturbances) that may be associated with CVA: • Recommend following the Advanced Cardiac Life Support (ACLS) Adult Suspected Stroke Algorithm that includes time-sensitive assessment and rtPA use guidance[a]. • Perform neurological imaging with DWI MRI as soon as feasible after the initial presentation of symptoms, preferably within 24 hours, or as indicated following an acute intervention. DWI MRI is preferred, but if contraindicated, alternative imaging modalities may be used. If imaging is consistent with a CVA, proceed to the following:	
1	For any new CVA event confirmed by imaging (DWI MRI preferred unless contraindicated), regardless of neurological symptoms (eg, cryptogenic CVA), and for suspected TIA without clear alternative etiology: • Discontinue study treatment for patients receiving bempegaldesleukin in combination with a checkpoint inhibitor (ie, nivolumab).
2	Neurology consultation recommended.
3	Perform pertinent laboratory assessments including coagulation (D-dimer, complete blood count with differential, serum blood urea nitrogen, and creatinine) [redacted]
4	Consider cardiac echocardiogram (trans-esophageal as appropriate) to evaluate for potential source of emboli.

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

a. ACLS-algorithms.com. Adult Stroke Algorithm, (ACLS) Advanced Cardiac Life Support [Internet]; 2021 [cited 5 May 2021]. Available from: https://acls-algorithms.com/adult-stroke-algorithm/. Additional consideration to the above CVA management guidelines for adolescent study population: rtPA use is not approved in this age group for acute ischemic stroke indication. Follow age-appropriate institutional guidelines for antithrombotic therapies for emergency ischemic stroke management.

APPENDIX 7: CYTOKINE RELEASE SYNDROME (CRS) MANAGEMENT ALGORITHM

A management algorithm for cytokine-release syndrome (CRS) for patients treated with bempegaldesleukin is provided below. This general guideline constitutes guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor.

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 guidelines (e.g., hydration management guidelines in Section 5.3.3.2).
- 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 (e.g., 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 (e.g., 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	

CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; ICU = intensive care unit; IV = intravenous; O_2 = oxygen; PO = oral.