Nektar Therapeutics

STATISTICAL ANALYSIS PLAN

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

Protocol Number: 20-214-29, Amendment 1.0

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
AUC	area under the drug concentration-time curve
bempegaldesleukin	International Nonproprietary Name (INN) for NKTR-214
BICR	blinded independent central review
CI	confidence interval
CL	clearance
Cmax	maximum observed concentration
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CVA	cerebrovascular accident
DMFS	distant metastasis-free survival
EDC	electronic data capture
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
eSAE	electronic serious adverse event
FPFV	first patient first visit
GCP	Good Clinical Practice
GH/QoL	global health/quality of life
HR	Hazard ratio
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IRT	Interactive Response Technology
IV	intravenous
kg	kilogram

Abbreviation	Definition
LN	lymph node
mg	milligram
min	minute(s)
mL	milliliter
NCI	National Cancer Institute
NED	no evidence of disease
NKTR-214	bempegaldesleukin (International Nonproprietary Name [INN] for NKTR-214)
OS	overall survival
PD	pharmacodynmanic
PD-L1	programmed cell death ligand 1
PFS2	Progression-free survival after the next line of treatment
PK	pharmacokinetic
PPK	process performance index
PROs	patient-reported outcomes
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
QoL	quality of life
RFS	recurrence-free survival
SAE	serious adverse event
SAP	statistical analysis plan
Tmax	time to maximum plasma concentration
ULN	upper limit of normal
US	United States
VAS	visual analog scale
Vd	volume of distribution

1.0 ADMINISTRATIVE STRUCTURE

This study will be managed via partnership between Nektar Therapeutics and a contract research organization (CRO). An interactive response technology (IRT) service provider will manage the randomization system, study drug, and comparator distribution and inventory management. Data for this trial will be entered into an Electronic Data Capture (EDC) system, using a Medidata Rave platform.

2.0 INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical methods to be implemented during the analyses of the data collected within the scope of Nektar Therapeutics Protocol 20-214-29 (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). The purpose of this SAP is to provide details on the analyses. Any deviations from the SAP will be documented in the clinical study report (CSR).

This Phase 3 study is conducted in accordance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

On 14 April 2022, Nektar Therapeutics and Bristol-Myers Squibb jointly decided to end the global clinical development program for bempegaldesleukin. This study and all other ongoing studies in this program will be discontinued.

3.0 STUDY OBJECTIVES

This section shows planned primary, secondary and exploratory objectives from the study protocol. However, due to early study termination, no blinded independent central review (BICR) data is available, thus the analyses for the primary endpoint of recurrence-free survival (RFS) by BICR, and the analyses for the secondary endpoints of distant metastasis-free survival (DMFS) by BICR and association between PD-L1 expression status and RFS by BICR will not be performed in the final study CSR. Descriptive analyses for the secondary endpoint of RFS by investigator and other secondary endpoints will be done based on available data. All comparative analyses comparing Arm B vs Arm A will not be conducted.

Due to early study termination, analyses and parameter calculations specified in the protocol for pharmacokinetic (PK), immunogenicity, biomarker (except PD-L1), clinical laboratory are no longer planned to be conducted. Other analyses no longer planned to be performed are vital signs, physical examination, electrocardiogram (ECG), concomitant medications, other safety observations for bempegaldesleukin, prior medications, prior therapy (cancer-related radiotherapy, systemic therapy), prior melonoma-related surgery, medical history, post-study cancer therapy and important protocol deviations. The analyses for all exploratory endpoints will not be performed.

3.1 Primary Objectives

- To compare RFS by BICR, of bempegaldesleukin (NKTR-214) plus nivolumab versus nivolumab monotherapy 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 overall survival (OS) of bempegaldesleukin (NKTR-214) plus nivolumab versus nivolumab monotherapy 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 (NKTR-214) plus nivolumab versus nivolumab monotherapy

- To assess the overall safety and tolerability of bempegaldesleukin (NKTR-214) plus nivolumab versus nivolumab monotherapy 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 (NKTR-214) plus Nivolumab versus Nivolumab monotherapy in patients with completely resected Stage IIIA (LN metastasis > 1 mm), Stage IIIB/C/D, or Stage IV NED melanoma

4.0 STUDY ENDPOINTS

This section shows planned primary, secondary and exploratory endpoints from the study protocol. However, due to early study termination, no blinded independent central review (BICR) data is available, thus the analyses for the primary endpoint of recurrence-free survival (RFS) by BICR, and the analyses for the secondary endpoints of distant metastasis-free survival (DMFS) by BICR and association between PD-L1 expression status and RFS by BICR will not be performed in the final study CSR. Descriptive analyses for the secondary endpoint of RFS by investigator and other secondary endpoints will be done based on available data. All comparative analyses comparing Arm B vs Arm A will not be conducted.

Due to early study termination, analyses and parameter calculations specified in the protocol for pharmacokinetic (PK), immunogenicity, biomarker (except PD-L1), clinical laboratory are no longer planned to be conducted. Other analyses no longer planned to be performed are vital signs, physical examination, electrocardiogram (ECG), concomitant medications, other safety observations for bempegaldesleukin, prior medications, prior therapy (cancer-related radiotherapy, systemic therapy), prior melonoma-related surgery, medical history, post-study cancer therapy and important protocol deviations. The analyses for all exploratory endpoints will not be performed.

4.1 Primary Efficacy Endpoints

- RFS, 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.

4.2 Secondary Efficacy Endpoint

- OS, defined as time from randomization to the date of death from any cause. Patients who do not have a date of death will be censored at their last known alive date.

- 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. Patients who were alive and without progression after the next line of therapy can be censored at last known alive date.
- Overall safety and tolerability will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities in the safety population
- PROs will be measured by 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 will be measured by the RFS by BICR endpoints based on PD-L1 expression level.
- RFS by investigator, defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis by investigator), new primary melanoma (by investigator), or all-cause death, whichever occurs first.

5.0 OVERALL STUDY DESIGN AND PLAN

5.1 Study Design

This is a multicenter, randomized, open-label, Phase 3 study that will evaluate the efficacy and safety of bempegaldesleukin(NKTR-214) 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 to the two treatment arms below:

- Arm A: bempegaldesleukin(NKTR-214) plus Nivolumab IV infusion q3w
- Arm B: Nivolumab IV infusion q4w

Randomization will be stratified by:

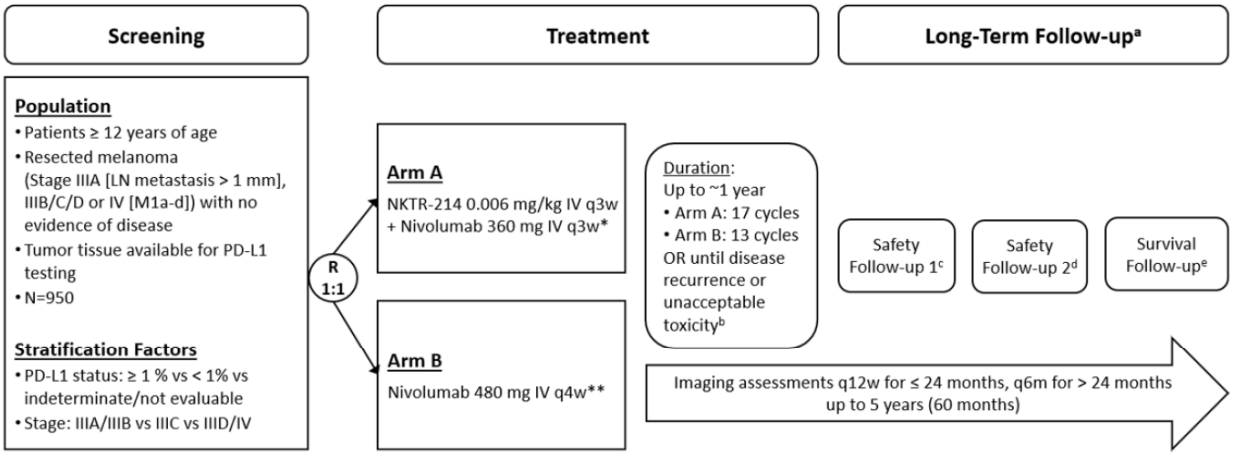
- PD-L1 status by Dako PD-L1 PharmDx 28-8 assay: ≥ 1% vs < 1% vs indeterminate/not evaluable

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

Figure 1 displays the study schematic.

On 14 April 14 2022, Nektar Therpautics and Bristol-Myers Squibb jointly decided to end the global clinical development program for bempegaldesleukin in combination with Nivolumab. This study has been terminated from this decision. As of the date of announcement, approximately 774 patients were enrolled and the data for those patients will be limited due to early termination, thus not all analyses described in the protocol will be performed. The details for the planned analyses for this final CSR are included in Section 6 and Section 7.

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.

5.2 Study Medications

Within 5 calendar days following randomization, the patient should receive the first dose of study treatment. Table 1 provides the timing of study drug administration.

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.

Table 1 Tumor Tissue Collection Schedule

Treatment Arm	Study Treatment	Starting Dose	Frequency of Administration	Route of Administration
Arm A[a]	Bempegaldesleukin	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.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

5.2.1 Arm A: Bempegaldesleukin Dosing

Each patient's bempegaldesleukin (NKTR-214) 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 (NKTR-214) 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.

Bempegaldesleukin treatment can continue for patients randomized to the bempegaldesleukin and nivolumab combination arm if nivolumab is permanently discontinued due to toxicities.

5.2.2 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.

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

5.3 Pharmacokinetic (PK) and Immunogenicity Measurements

Only limited plasma PK samples for NKTR-214-RC were analyzed before study termination, all other PK and immunogenicity sample assessments as described in study protocol were not performed due to early study termination.

6.0 STATISTICAL CONSIDERATIONS

6.1 General Considerations

Summary statistics for continuous variables will include the mean, standard deviation, median, minimum, and maximum. The mean and median will be presented to one decimal place beyond which the data were captured. The standard deviation will be presented to two decimal places beyond which the data were captured. The minimum and maximum will be presented to the precision with which the data were captured.

Categorical variables will be presented as frequency counts and percentages. A row or column denoted 'Missing' will be included in count tabulations where necessary to account for dropouts and missing values. Percentages will be rounded to 1 decimal place and the percent will be suppressed when the count is zero. The denominator will be the number of patients in the population of interest unless otherwise noted.

Data listings will be created to support each table and to present all data. Data listings will be presented by treatment group and patient number.

6.2 Determination of Sample Size

Up to 950 Stage III/IV melanoma patients at high risk of recurrence will be randomized into the two arms (N 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. 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.

A grou sequential testing procedure wll be employed with two interim analyses at approximately 320 events (80% of the targeted RFS events for final analysis) are observed, which is expected to be 42 months from FPFV, and 360 events (90% of the targeted RFS events for final analysis) are observed, which is expected to be 54 months from FPFV. The O'Brien and Fleming boundaries will be utilized in this analysis for the rejection of null hypothesis to maintain an overall nominal significance level of 0.05(two-sided). The boundary values for the regect of null hypothesis are given in Table 2.

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

Table 2 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.				

6.3 Analysis Populations

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.

Due to early termination of this study, all analyses in this SAP will be performed on Safety Population.

6.4 Handling of Missing Data

- Missing dates will be handled as follows:For subsequent anti-cancer therapy start date:
  - If only day is missing then: if end date of subsequent anti-cancer therapy is complete, impute to the minimum of (the last day of the month, end date of subsequent anti-cancer therapy); otherwise impute to the last day of the month.
  - If month or year is missing then leave missing.

- For time from initial diagnosis to randomization and time from diagnosis of metastatic disease to randomization, partial dates for initial diagnosis and diagnosis of metastatic disease will be imputed as follows:
  - No imputation will be done if the year is missing
  - If the year is before randomization date then missing days will be imputed as the first day of the month and missing months will be imputed as July
  - If the year is the current year of randomization date then missing days will be imputed as the first day of the month and missing months will be imputed as January
- For duration of AEs, partial dates for **start** of AE will be imputed as follows:
  - Missing day, month, and year should be queried. In case of non-resolution of missing year, then the missing day will be imputed as Cycle 1 Day 1 (C1D1).
  - Start day of AE is missing and the year is same as Cycle 1 Day 1 (C1D1)
    - If the reported month of occurrence of AE is after the month of C1D1 dose then missing day will be imputed as the first day of the month of occurrence of AE.
    - If the reported month of occurrence of AE is the month of C1D1 dose then the missing day will be imputed as the same day as C1D1.
    - If the reported month of AE start date is before the month of C1D1 then the missing day will be imputed as day 15 of the month of AE start date.
    - If the month of AE start date is missing, missing day will be imputed as the date of C1D1.
  - Start day of AE is missing and the year is after the year of C1D1
    - Missing day will be imputed as the first day of the month of occurrence of AE
    - If the month of AE start date is missing, missing day will be imputed as 01 January of the year of AE start date.
- For duration of AEs, partially missing dates for **stop** of AE will be imputed as follows:
  - If the stop date is completely missing, it should be queried. In case of non-resolution of missing year, no imputation will be performed.
  - If only the day is missing, the earlier of the following will be used as the stop date:
    - the last day of the month for stop of AE
    - the later of (last known alive date, AE start date if imputed)

  - If month and day are missing, the earlier of the following will be used as the stop date:
    - December 31st of the year for stop of AE
    - the later of (last known alive date, AE start date if imputed)

- For determination of prior medication, any medication with a start date prior to C1D1 will be classified as prior medication regardless of the stop date. Missing or partial dates will be handled as follows:
  - If missing day and/or month of the start date, the medication will be classified as prior unless the month and/or year of the start date is after C1D1
- For determination of concommitant medication, the following will be classified as concomitant medication:
  - Any medication with a start date prior to or on C1D1 and continued after C1D1 (this will be considered as both prior and concomitant medication)
  - Any medication with a start date after C1D1, but prior to the last dose date + 100 days or (date of initiation of subsequent anti-cancer therapy – 1 day), whichever is earlier
- Missing or partial dates for concomitant medication will be handled as follows:
  - If missing day and/or month of the start date, the medication will not be considered as concomitant if the month and/or year of the start date is after the last dose date + 100 days or (date of initiation of subsequent anti-cancer therapy – 1 day), whichever is earlier
  - If missing day and/or month of the stop date, the medication will not be considered as concomitant if the month and/or year of the stop date is prior to C1D1
  - A medication with completely missing start and stop dates will be classified as concomitant
- In order to calculate duration of immune modulating medication for management of drug-related select AEs or IMAEs (as defined in Section 7.2), missing or partial dates for these medications will be handled as follows:

  Missing or partial start date:

  - If the start date is completely missing, it will not be imputed. Only the number of days that the medication was taken on or after the AE start date will be counted toward the duration of IMM for management of certain AE.
  - If only year is provided, impute the start date to January 1st of the year,
  - If only day is missing, impute the start date to the first day of the month.

Missing or partial stop date:

- If the stop date is completely missing, impute stop date to the later of (last known alive date, AE start date if imputed)
- If only the day is missing, the earlier of the following will be used as the stop date:
  - the last day of the month for stop of AE
  - the later of (last known alive date, AE start date if imputed)
- If month and day are missing, the earlier of the following will be used as the stop date:
  - December 31st of the year for stop of AE
  - the later of (last known alive date, AE start date if imputed)

- For death date, the following conventions will be used:
  - If the death date is completely missing but reason for death is present, it will be imputed as the last known alive date
  - If the the death date is partially missing (missing day only, or missing both day and month), the death date and corresponding last known alive date will be imputed in 2 steps:
    1. Imputed as 1st of month (missing day only) or January 1st of the year (missing both day and month)
    2. The imputed death date from the 1st step will be compared to the latest alive date captured from multiple sources (unimputed last known alive date), and the maximum of the two will be considered as the imputed death date and last known alive date

No imputation of other missing data is planned.

6.5 Stratification and Pooling

For stratified analyses, the randomization stratification factors entered into the IRT system at the time of randomization will be used, as follows:

- PD-L1 status by Dako PD-L1 PharmDx 28-8 assay: $\geqslant$ 1% vs < 1% vs indeterminate/not evaluable.

  Note: PD-L1 indeterminate/not evaluable will be capped at a maximum of 25% of the total

- Stages of Disease per AJCC 8th edition are stratified as follows: Stage IIIA (LN metastasis > 1 mm)/IIIB vs IIIC vs IIID/IV.

6.6 Definitions

- Baseline: In general, baseline will be defined as the last assessment result on or before the randomization date (and time if available).

  Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment.

- Study Day: There is no study day zero. In general, Study Day 1 is the date of randomization.
  - For post-randomization days, study day is calculated as: assessment date – randomization date + 1
  - For pre-randomization days, study day is calculated as: assessment date – randomization date

  For safety analysis, study day is calculated and presented based on first dose date as defined below.

- First Dose Date: First dose date will be defined as the date of first dose, Cycle 1 Day 1 (C1D1). Note, per protocol, first dose date may be ≤ 5 days after the date of randomization. If randomization date and first dose date is not on the same day, then date of randomization will be different from C1D1. Safety data will be calculated and presented based on First Dose Date.

- Treatment-emergent/Extended Treatment-emergent Period:

  For patients on treatment, both the treatment-emergent period and extended treatment-emergent period will be defined as the period of time on or after the day (and time, if collected and not missing) of the first dose of study treatment.

  For patients off treatment, the treatment-emergent period is defined as the period of time on or after the day (and time, if collected and not missing) of the first dose of study treatment, until: earlier date of (initiation of new anticancer therapy – 1 day) and (30 days after the date of the last dose of any study treatment).

  The extended treatment-emergent period will be defined as the period of time on or after the day (and time, if collected and not missing) of the first dose of study treatment, until earlier date of (initiation of new anticancer therapy – 1 day) and (100 days after the date of the last dose of any study treatment)

- Treatment-Emergent Adverse Event (TEAE):

TEAEs are AEs with onset date (and time, if collected and not missing) within the treatment-emergent period, or extended treatment-emergent period depending on the analysis

Incomplete start and end date for TEAEs will be imputed. Any AE will be considered as a TEAE if its status cannot be fully determined because of incomplete data.

- Last Known Alive Date: Last known alive date will be defined as the latest alive date on or before data cutoff date, captured from multiple sources. Note that if there is an event date (either an assessment or death) beyond data cutoff date, the last known alive date will be the data cutoff date. If a patient died before or on cutoff date, last known alive date will be set as the death date. Last known alive date will not be imputed, except in the case that the death date is partially missing (see details in section 6.4)

6.7 Study Drug Exposure

Analyses will be performed by treatment group "as treated" in Safety Population, unless otherwise specified.

6.7.1 Administration of Study Drug

The following parameters will be calculated:

- Number of cycles: Total number of complete or partial treatment cycles the patient received
- Total number of infusions: Total number of infusions for which the patient received non-zero dose across all cycles
- Average duration of infusion (min): Total infusion time (min) / Total number of infusions; where total infusion time = summation of (completion time of infusion – start time of infusion) for all infusions of a patient
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- Duration of study treatment (days): Date of last dose – date of first dose (C1D1) + 1

To present duration of study treatment using a Kaplan-Meier curve, the last dosing date will be the event date for those participants who are off study drug. Median duration of study therapy and associated 95% CI will be provided. Participants who are still on study drug will be censored on their last dosing date.

Table 3 Arm A: Bempegaldesleukin+ Nivolumab Parameter Definitions

	Bempegaldesleukin	**Nivolumab**	
		Nivolumab (mg)	**Nivolumab (mg/kg) (Patients < 40 kg)**
Dosing Schedule per Protocol	0.006 mg/kg Q3W	360 mg Q3W	4.5 mg/kg Q3W
Dose	Dose (mg/kg) is defined as total dose administered at each dosing date (mg) divided by the most recent weight (kg). Dose administered and weight are collected from the CRF	Dose (mg) is defined as the total drug administrated at each dosing date as collected on the CRF	Dose (mg/kg) is defined as total dose administered at each dosing date (mg) divided by the most recent weight (kg). Dose administered and weight are collected from the CRF
Cumulative Dose	Cumulative Dose (mg/kg) is the sum of the doses administered to a participant during the treatment period	Cumulative Dose (mg) is sum of all doses administered to a participant during the treatment period	Cumulative Dose (mg/kg) is the sum of the doses administered to a participant during the treatment period
Relative Dose Intensity (%)	Cumulative dose (mg/kg)/[0.006 x (Last dose date - Start dose date + 21)/21] x 100	Cumulative dose (mg) /[(Last dose date - Start dose date + 21) x 360 /21] x 100	Cumulative dose (mg/kg) /[4.5x (Last dose date - Start dose date + 21) /21] x 100
Actual Dose Intensity	Actual dose intensity (mg/kg/week): [Cumulative dose (mg/kg) / (Exposure duration (in days) + 20 days)] × 7	Actual dose intensity (mg/week): [Cumulative dose (mg) / (Exposure duration (in days) + 20 days)] × 7	Actual dose intensity (mg/kg/week): [Cumulative dose (mg/kg) / (Exposure duration (in days) + 20 days)] × 7

Table 4 Arm B: Nivolumab Parameter Definitions

	Nivolumab	
	Nivolumab (mg)	**Nivolumab (mg/kg) (Patients < 40 kg)**
Dosing Schedule per Protocol	480 mg Q4W	6.0 mg/kg Q4W
Dose	Dose (mg) is defined as the total drug administrated at each dosing date as collected on the CRF	Dose (mg/kg) is defined as total dose administered at each dosing date (mg) divided by the most recent weight (kg). Dose administered and weight are collected from the CRF
Cumulative Dose	Cumulative Dose (mg) is sum of all doses administered to a participant during the treatment period	Cumulative Dose (mg/kg) is the sum of the doses administered to a participant during the treatment period
Relative Dose Intensity (%)	Cumulative dose (mg) /[(Last dose date - Start dose date + 28) x 480 /28] x 100	Cumulative dose (mg/kg) /[6x (Last dose date - Start dose date + 28) /28] x 100
Actual Dose Intensity	Actual dose intensity (mg/week): [Cumulative dose (mg) / (Exposure duration (in days) + 27 days)] × 7	Actual dose intensity (mg/kg/week): [Cumulative dose (mg/kg) / (Exposure duration (in days) + 27 days)] × 7

6.7.2 Modifications of Study Therapy

Per protocol, for bempegaldesleukin, dose reduction is permitted (as specified in the protocol). This information will be retrieved from CRF dosing pages.

- For participants treated with bempegaldesleukin (NKTR-214), the following will be summarized: Number of participants with dose reduction along with the reason of the dose reduction

Per protocol, for bempegaldesleukin and nivolumab dose delay is permitted (as specified in the protocol).

- Number of participants with dose delay along with the reason of the dose delay

6.8 Patient Disposition

A summary of patient disposition will display the number of patients who were randomized by treatment arm. In addition, the number of patients who discontinued study drug and the number of patients who exited the study, both overall and by reason, will be performed by treatment arm for the Safety population. Descriptive statistics for time to study drugs (bempegaldesleukin, nivolumab, bempegaldesleukin or nivolumab) discontinuation (mean, median, min, max) will be summarized for the patients who discontinued study drugs. The follow-up time (time from randomization to the last known alive or death date) will be summarized.

All disposition data will be performed in a data listing.

6.9 Study Population

6.9.1 Demographics and Other Baseline Disease Characteristics

The following baseline data will be summarized and listed by treatment arms for Safety population:

- Age
- Age categorization (< 65 vs ≥ 65, < 75 vs ≥ 75)
- Gender
- Ethnicity
- Race
- ECOG
- Geographic region (North America, EU vs. Rest of the world)

6.9.2 Randomization Stratification Factors

Randomization stratification factors will be summarized for the Safety population by treatment arms.

- PD-L1 Status as Randomized (≥ 1% vs < 1% vs indeterminate/not evaluable) as per EDC.
- Stage as randomized (IIIA (LN metastases > 1 mm)/IIIB vs IIIC vs IIID/IV) as per EDC.
- Stratification Factor as Randomized as per EDC

≥ 1% – IIIA (LN metastases > 1 mm)/IIIB vs ≥ 1% – IIIC vs ≥ 1% – IIID/IV

< 1% – IIIA (LN metastases > 1 mm)/IIIB vs < 1% – IIIC vs < 1% – IIID/IV

Indeterminate/non-evaluable – IIIA (LN metastases > 1 mm)/IIIB vs Indeterminate/non-evaluable – IIIC vs Indeterminate/non-evaluable – IIID/IV

The randomization stratification factors will be listed as per EDC and per IRT. The number of subjects randomized by country will also be summarized.

6.10 Treatments and Medications

6.10.1 Concomitant Medications

The planned analysis for concomitant medication as described in the protocol will not be performed in this final CSR due to the early termination of this study as a consequence of the closure of the bempegaldesleukin clinical program.

6.10.2 Study Drug Exposure

Overall exposure to each study drug will be summarized for the Safety population. Overall exposure to study drugs will be summarized in terms of exposure duration, number of cycles, and relative dose intensity. The following summaries will also be performed:

- Time from randomization to first dose of study therapy (0 to 3 days, > 3 to 7, > 7 to 14, > 14 to 21, > 21)
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%
- Overall exposure duration
- Overall cumulative dose
- Number of cycles completed
- Number of infusions
- Average duration of infusion
- Dose-intensity
- The number of patients with at least one dose infusion interruption, the reason for interruption, and the number of infusion interruptions per patient
- The number of patients with at least one dose delay (either study drug) or dose reduction (for bempegaldesleukin only) and their reason(s)

All study exposure data will be performed in a data listing.

6.11 Efficacy Analysis

Due to early termination of the study, all comparative analyses comparing Arm B vs Arm A will not be conducted. Only descriptive analyses by treatment arm will be provided if applicable.

6.11.1 Efficacy Analysis of Primary Endpoints

There is no BICR data transferred for this study due to the early termination of this study as a consequence of the closure of the bempegaldesleukin clinical program. Thus, the planned analysis for the primary efficacy endpoint (RFS by BICR) as described in the protocol will not be performed.

6.11.2 Efficacy Analysis of Secondary Endpoints

6.11.2.1 Overall Survival

The key secondary endpoint of OS is defined as time from randomization to the date of death from any cause. Patients who do not have a date of death will be censored at their last known alive date. Patients will be followed until their date of death, loss to follow-up, or withdrawal of consent for further follow-up for survival. Patients who do not have any follow-up since randomization will be censored on the date of randomization.

The analysis of OS in the safety population will be conducted by summarizing the number of events, and the descriptive statistics (median and its 95% CI, Q1, Q3, minimum, maximum) based on the Kaplan-Meier estimate will also be summarized by treatment arm. The overall survival rates at 6 and 12 months will be performed by treatment arm.

By-subject listing of OS will be provided.

6.11.2.2 Distant Metastasis-Free Survival

There is no BICR data transferred for this study due to the early termination of this study as a consequence of the closure of the bempegaldesleukin clinical program. The analysis for DMFSby BICR will not be performed in theCSR.

DMFS by investigator is 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. The analysis of DMFS by investigator in the Safety population will be conducted by summarizing the

number of events, and the descriptive statistics (median and its 95% CI, Q1, Q3, minimum, maximum) based on the Kaplan-Meier estimate will also be summarized by treatment arm. The DMFS rates at 6 and 12 months will be performed by treatment arm.

6.11.2.3 Progression-Free Survival 2

PFS on next-line therapy (PFS2) is defined as the time from randomization to documented progression, per investigator assessment, after the next line of therapy or to death from any cause, whichever occurs first. Patients who were alive and without progression after the next line of therapy will be censored at last known alive date. The following censoring rules will be applied for PFS2:

For a patient who did not receive subsequent anti-cancer therapy:

- If the patient died, the patient is considered as an event on the date of death
- Else, the patient is censored at his/her last known alive date

For a patient who received subsequent anti-cancer therapy:

- If the patient had disease progression after the start of subsequent anti-cancer therapy, the patient is considered as an event on the date of PD
- Else if the patient died or started a second subsequent anti-cancer therapy, the patient is considered as an event at the death date or at the start date of second subsequent therapy whichever is the earliest.
- Else, the patient is censored at his/her last known alive date

The PFS2 by investigator in the safety population will be conducted by summarizing the number of events, and the descriptive statistics (median and its 95% CI, Q1, Q3, minimum, maximum) based on the Kaplan-Meier estimate will also be summarized by treatment arm. The PFS2 rate at 6, and 12 months will be performed by treatment arm.

6.11.2.4 PD-L1 Expression as a Predictive Biomarker for RFS per BICR

There is no BICR data transferred for this study due to the early termination of this study, which resulted from the decision to end the global clinical development program for bempegaldesleukin in combination with Nivolumab. Thus, the planned analysis for PD-L1 expression as a predictive biomarker for RFS per BICR as described in the protocol will not be performed.

6.11.2.5 Patient-Reported Outcomes (PROs)

The analysis of EORTC QLQ-C30 data will be performed in the Safety population. 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).

The primary time point of interest will be Day 1 of Cycle 1 and Day 1 of Cycle 2-17 for Arm A, and Day 1 of Cycle 1 and Day 1 of Cycle 2-3 for Arm B.

6.11.2.6 Recurrence-free Survival (RFS) by Investigator

RFS by investigator is defined similar to the primary endpoint, but recurrence and new primary melanoma are decided by Investigator. It is defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis by investigator), new primary melanoma (by investigator), 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 5.

Table 5 Censoring Scheme for 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

The RFS by investigator in the Safety population will be conducted by summarizing the number of events, and the descriptive statistics (median and its 95% CI, Q1, Q3, minimum, maximum) based on the Kaplan-Meier estimate will also be summarized by treatment arm. The RFS rates at 6 and 12 months will be presented by treatment arm.

7.0 SAFETY ANALYSIS

The safety data will include AEs and SAEs. Summaries will use Safety population and will be performed separately by treatment arm. All safety data will be presented in data listings.

7.1 Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. Adverse event severity will be based on NCI CTCAE Grade (version 5.0).

All AEs will be coded by MedDRA version 21.1. The severity of AE will be determined based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade (version 5.0). An AE is considered as related to treatment if it is related to any study drug; an AE with a missing relationship will be counted as related to study drug. An AE is considered as leading to treatment discontinuation if it is leading to discontinuation of any study drug. An AE is considered as leading to treatment delay, reduction or interruption if reported as leading to the dose delay, reduction or interruption of any study drug. An AE is considered as leading to death if the severity grade is 5 or the outcome is fatal. A patient reporting the same AE multiple times will be counted only once within each SOC and PT under the highest severity and closest relationship.

The following adverse events summaries will be provided by treatment arm:

- Overall summary of TEAEs
- TEAEs presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT
- Serious TEAEs presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT
- Drug-related TEAEs presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT
- TEAEs leading to any study drug discontinuation presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT
- TEAEs leading to death presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC and PT
- Grade 3 or above TEAE by by SOC and PT

All AEs will be presented in listing as follows:

- All TEAEs
- SAEs
- Grade 3 or above TEAEs
- TEAE leading to any study drug discontinuation
- TEAEs leading to death

7.2 Immune Mediated Adverse Events (IMAEs)

Immune-mediated AEs (IMAE) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. To be specific, IMAEs are events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator that meet the definition summarized below:

- those occurring within extended treatment-emergent period,
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine AEs such as adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication),
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component

The list of MedDRA preferred terms used to identify IMAEs is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided. IMAEs will be summarized using the extended treatment-emergent period by treatment arm for each immune-mediated category:

- Overall summary of non-endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT.

- Overall summary of endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT

A by-patient listing of IMAEs will be provided.

7.3 Other Immune-Related Adverse Events of Special Interest (OirAESIs) for Checkpoint Inhibitors

Other immune-related events of special interest (OirAESIs) for checkpoint inhibitors consist of a list of preferred terms grouped by specific category (e.g., Myositis Event, Myocarditis Event, Demyelination Event, Guillain-Barre Syndrome, Pancreatitis Event, Uveitis Event, Encephalitis Event, Myasthenic Syndrome, Rhabdomyolysis Event, Graft Versus Host Disease).

The list of MedDRA preferred terms used to identify OirAESI is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

OirAESIs will be summarized by treatment arm for each category. The following analyses will be conducted using the extended treatment-emergent period:

- Overall summary of OirAESIs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT

A by-patient listing of OirAESIs will be provided.

7.4 Adverse Events of Special Interest for bempegaldesleukin (NKTR-214)

Adverse events of special interest for bempegaldesleukin (NKTR-214) consists of ischemic cerebrovascular events (ICE). All analyses will be conducted in the Safety population by treatment arm using the treatment-emergent period. Search list used to identify ICE will be provided.

The following analyses will be conducted for ICE:

- Overall summary of ICE by worst CTC grade (any grade, grade 3-4, grade 5) presented by PT

A by-patient listing of ICE will be provided.

7.5 Clinical Laboratory, Vital Signs, Physical Examination and Electrocardiogram

The planned analyses on clinical laboratory, vital signs, physical examination and electrocardiogram described in the protocol will not be analyzed due to early study termination.

8.0 DATA MONITORING COMMITTEE

An external multidisciplinary Data Monitoring Committee (DMC) will be convened for this study. The DMC will be comprised of qualified clinicians and a biostatistician, all independent from the Sponsor and (for the clinicians) independent of investigational sites, selected to avoid conflict(s) of interest. The DMC's specific activities will be detailed in a mutually agreed upon charter, which will define the relevant processes, including meeting proceedings and structure, data assessments, documentation and recordkeeping, process for DMC recommendations, and regulatory reporting, as applicable. The charter will contain procedures to ensure the minimization of bias, such as maintaining confidentiality of any interim data.

The DMC will review the results of the interim analyses as well as assess accumulating safety data and emerging risk/benefit balance at regular intervals and on an ad-hoc basis as detailed in the DMC charter. The DMC will also conduct the OS events re-estimation; details will be provided in the DMC charter.

Due to the early termination of this study as a consequence of the closure of the bempegaldesleukin clinical program, the DMC has been dissolved.

9.0 PHARMACOKINETIC AND IMMUNOGENICITY ANALYSES

The planned analyses on PK and immunogenicity data described in the protocol will not be analyzed due to early study termination.

10.0 INTERIM ANALYSIS

There are two planned interim analyses for the study, but none was performed due to early study termination.

11.0 REFERENCES

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2. Musoro JZ, Bottomley A, Coens C, Eggermont AM, King MT, Cocks K, Sprangers MA, Groenvold M, Velikova G, Flechtner HH, Brandberg Y; EORTC Melanoma Group and EORTC Quality of Life Group. Interpreting European Organisation for Research and Treatment for Cancer Quality of life Questionnaire core 30 scores as minimally importantly different for patients with malignant melanoma. Eur J Cancer. 2018 Nov;104:169-181. doi: 10.1016/j.ejca.2018.09.005. Epub 2018 Oct 22. PMID: 30359910.

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