Phase 1 Study of VE800 and Nivolumab in Patients with Selected Types of Advanced or Metastatic Cancer

NCT04208958

Submitter: John Caccaviello, MS – Clinical Trial Associate at Vedanta Biosciences

Included in this submission:

Redacted Statistical Analysis Plan (Version 1.2. 03MAR21)

Document Date: 29AUG22

Statistical Analysis Plan (SAP)

Protocol Title:	Phase 1 Study of VE800 and Nivolumab in Patients with Selected Types of Advanced or Metastatic Cancer
Protocol Version No./Date:	2.0 / 11-DEC-2019
CRF Version No./Date:	1.1 / 11-FEB-2020
SAP Version No./Date:	1.2 / 03-MAR-2021

1.0 Approvals

Sponsor	
Sponsor Name:	Vedanta Biosciences, Inc.
Representative / Title:	[redacted]
Signature / Date:	
[redacted]	
Biostatistician / Title:	[redacted]
Signature / Date:	

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

2.0 Change History

Version/Date	Change Log
V1.0 / 12-Mar-2020	Created as new
V0.2 / 22-Apr-2020	Update 1
V0.3 / 12-May-2020	Update 2
V0.4 / 13-May-2020	Update 3 with changes discussed at SAP meeting with Vedanta
V1.0 / 30-Jun-2020	Final Version for Approval
V1.0 / 23-July-2020	Final Version for Approval after revisions requested from 30-Jun-20 version
V1.1 / 15-Nov-2020	[redacted]
V2.0/ 03-Mar-2021	[redacted]

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Vedanta Biosciences Protocol VE800-001.

5.0 Scope

The Statistical Analysis Plan outlines the study design and objectives, analysis endpoints and subject sets, applicable study definitions, and statistical methods.

6.0 Introduction

This SAP should be read in conjunction with the study protocol and case report form (CRF) versions noted on the title page. Any further changes to the protocol or CRF may necessitate updates to the SAP. Final approval of the SAP by the Sponsor [redacted] will occur prior to the database lock.

[redacted]

7.0 Study Objectives

Primary objectives:

- To evaluate the safety and tolerability of VE800 in combination with nivolumab in terms of adverse events (AE) rates using Common Terminology Criteria for Adverse Events (CTCAE, v. 5.0)
- To evaluate clinical activity as measured by objective response rate (ORR) of the study drug combination using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Secondary objectives:

- To evaluate additional measures of clinical benefit, including:
  - Duration of response (DOR) according to RECIST 1.1
  - Best overall response (BOR) according to RECIST 1.1
  - Disease control rate (DCR) according to RECIST 1.1
  - Progression-free survival (PFS) according to RECIST 1.1
  - Overall survival (OS)

Exploratory objectives:

- [redacted]

8.0 Study Design

This is a first-in-human multicenter, open-label study evaluating the safety and clinical activity of VE800 in combination with nivolumab in patients with selected types of advanced or metastatic cancer, where efficacy of an anti-PD-1 antibody is expected to be modest to null. Safety, clinical activity, PK, and pharmacodynamics (stool, blood and/or tumor biomarker changes) will be evaluated.

The following cohorts of patients with advanced/metastatic cancer will be enrolled:

- Melanoma

- Gastric/gastroesophageal junction (GEJ) adenocarcinoma
- Colorectal cancer microsatellite-stable (CRC-MSS)

[redacted]

All patients will continue study treatment until progression, unacceptable toxicity, withdrawal of consent, study discontinuation criteria are met, completion of 2 years of treatment, or the study ends, whichever occurs first. Patients benefiting from study treatment, as judged by the Investigator, may continue study treatment for up to 2 years.

[redacted]

In each disease-specific expansion cohort, a Simon two-stage design will be used to provide an initial assessment of the clinical activity at Stage 1. ORR will be evaluated using RECIST 1.1.

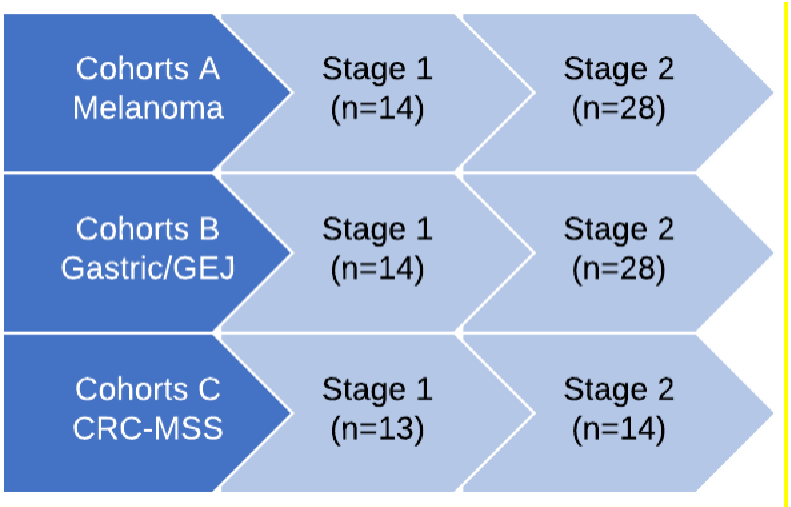

Figure 1 Flow Diagram of Study VE800-001—Simon Two-Stage Design

A total of up to approximately 111 patients will be enrolled at up to 45 centers in the United States (US).

8.1 Sample Size Considerations

The study will use a Simon two-stage design. In each disease-specific expansion cohort, a Simon two-stage design will be used to provide an initial assessment of the clinical activity at Stage 1 for continuation to Stage 2. ORR will be evaluated using RECIST 1.1.

In the melanoma and the gastric/GEJ adenocarcinoma cohorts, with an undesirable ORR of 10% or less, a desirable ORR of 25% or more, and Type 1 error rate of 10%, 42 patients give 85% power to detect the minimal desirable or indecision ORR of 25%. After the first stage (enrollment of 14 patients), enrollment (of another 28 patients) maybe discontinued to the second stage if less than 2 patients achieve objective response. The cohort will be declared a success at the end of the second stage if more than 6 patients achieve objective response.

Similarly, in the CRC-MSS cohort, with an undesirable ORR of 2% or less, a desirable ORR of 15% or more, and Type 1 error rate of 10%, 27 patients give 85% power to detect the minimal desirable or indecision ORR of 15%. After the first stage (enrollment of 13 patients), enrollment (of another 14 patients) maybe discontinued to the second stage if no patients achieve objective response. The cohort will be declared a success at the end of the second stage if more than 1 patient achieves objective response.

8.2 Randomization

This is an open-label, non-randomized study. Patients will be enrolled in cohorts based on cancer type.

9.0 Study Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of VE800 in combination with nivolumab in terms of AE rates using Common Terminology Criteria for Adverse Events, v. 5.0	• Number of subjects with adverse events by type, grade, seriousness and causality • Incidence of DLTs • Number of subjects discontinuing study treatment due to an adverse event
• To evaluate clinical activity as measured by objective response rate (ORR) of the study drug combination using RECIST 1.1	• ORR according to RECIST 1.1
Secondary	
• To evaluate additional measures of clinical benefit, including: − Duration of response according to RECIST 1.1 − Best overall response according to RECIST 1.1 − Disease control rate according to RECIST 1.1 − Progression-free survival according to RECIST 1.1 − Overall survival	• DOR according to RECIST 1.1 • Best overall response according to RECIST 1.1 • DCR according to RECIST 1.1 • PFS according to RECIST 1.1 • OS
[redacted]	

[redacted]

[redacted]

10.0 Conventions and Derivations

10.1 Baseline, Change from Baseline

Unless otherwise stated, baseline refers to the last assessment prior to the first dose of nivolumab and VE800. Unscheduled assessments preceding Study Day 1 (i.e., Cycle 1/Day 1 [C1/D1]) will be considered for baseline. If the assessment time is missing and there is no way to determine if the assessment occurred before or after the study drug administration, assessments on Study Day 1 will be considered for baseline.

10.2 Study Day Definition

Study day is defined as (study date – C1/D1 date + 1). C1/D1 is the planned start date for the first dose of nivolumab and VE800.

10.3 Treatment-Emergent Adverse Events Definition

A TEAE is an undesirable event not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following study treatment. AEs that begin after the first dose of any study treatment (vancomycin, nivolumab, or VE800) and prior to 28 days after the last dose of any study treatment and prior to the initiation of follow up systemic anti-cancer therapy are considered as TEAEs. Baseline signs and symptoms that change attribution or severity during the on-study period are TEAEs.

10.4 Missing Data Imputation

10.4.1 Imputation of Partial Dates

Below are rules for imputing missing or partial dates for analyses of AEs, prior/concomitant medications, and systemic anti-cancer therapy regimen, and radiation procedures. Though imputed for analyses, actual dates (missing or partial) will be reflected in listings. Otherwise, there will be no imputation of missing data values. Data on subjects who withdraw early will be summarized up until the time of withdrawal.

Stop date imputation will not be applied to ongoing AEs or concomitant medications. Missing or partial dates for AEs, prior/concomitant medications, systemic anti-cancer therapy, and radiation procedures will be imputed as follows:

- Start Date for AEs
    - If only the day is missing and the month and year are the same as the month and year of the first dose date of any study treatment (including vancomycin), then the day will be imputed with the day of the first dose date. Otherwise the day will be imputed with the first day of the event month.
    - If both the day and month are missing and the year is the same as the year of the first dose date of any study treatment (including vancomycin), then they will be imputed with the month and day of the first dose date. Otherwise they will be imputed as January 1st of the event year.
    - If the start date is completely missing, the date will be imputed with the first dose date of any study treatment (including vancomycin).
    - If the stop date is complete and the imputed start date is after the stop date, then the imputed start date will be set to the stop date.
- Start Date for Concomitant Medications, Systemic Anti-Cancer Therapy, and Radiation Procedures

  - If only the day is missing and the month and year are the same as the month and year of the first dose date of any study treatment (excluding vancomycin), then the day will be imputed with the day of the first dose date. Otherwise the day will be imputed with the first day of the event month.
  - If both the day and month are missing and the year is the same as the year of the first dose date of any study treatment (excluding vancomycin), then they will be imputed with the month and day of the first dose date. Otherwise they will be imputed as January 1st of the event year.
  - If the start date is completely missing, the date will be imputed with the first dose date of any study treatment (excluding vancomycin).
  - If the stop date is complete and the imputed start date is after the stop date, then the imputed start date will be set to the stop date.

- Stop Date
  - If only the day is missing and the month and year are the same as the month and year of the study discontinuation date, then the day will be imputed with the day of the study discontinuation date. Otherwise the day will be imputed with the last day of the event month.
  - If both the day and month are missing and the year is the same as the year of the study discontinuation then they will be imputed with the month and day of the study discontinuation date. Otherwise they will be imputed as December 31st of the event year.
  - If the stop date is completely missing, then it will be imputed with the study discontinuation date.
  - If the imputed stop date is greater than the last contact date, then the imputed stop date will be set to last contact date.

- Diagnosis date
  - If only the day is missing, day 1 of the diagnosis month will be imputed.
  - If day and month are missing, January 1 will be imputed.

10.4.2 Imputation of Laboratory Values with Character Symbol

Missing laboratory data will not be imputed. However, laboratory values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" for calculation of summary statistics and comparing to normal ranges. These values will still be displayed as "< x" or "> x" in the listings.

10.4.3 Imputation of Missing Treatment Emergent Adverse Event Causality

If causality is missing for any TEAE, it will be imputed as related to treatment.

10.4.4 Imputation of Missed VE800 Doses

When computing the cumulative VE800 exposure, if the number of returned capsules is missing, "were there any missed doses" is missing or "N", and the number of sequential days missed is missing or "0", then assume all doses dispensed were taken.

When computing the cumulative VE800 exposure, if "Were there any missed doses" is checked on the CRF page but the number of missed doses is missing:

- If the number of sequential days missed has been entered, use the number of sequential days missed as the number of missed doses.

- If both number of missed doses and number of sequential days missed are missing, then assume the patient did not get any doses during that period.

11.0 Analysis Sets

11.1 Full Analysis Set

All patients who were enrolled and received any dose of any study drug (vancomycin, VE800, or nivolumab). The Full Analysis Set will be the default analysis set for all analyses, unless otherwise specified.

11.2 Safety Set

All patients who were enrolled and received at least 1 dose of any study drug (VE800 or nivolumab). The Safety Analysis Set will be the primary set for the analysis of safety data.

11.3 DLT-Evaluable Population

The first 12 patients to complete the first 28 days of combination treatment of VE800 and nivolumab administration or experience a DLT. DLT-evaluable population will be used for DLT analysis.

11.4 Efficacy Population

All patients who receive one dose of the combination treatment of VE800 and nivolumab and have at least one tumor assessment (target) at baseline and at least one post-baseline overall RECIST response based on the Disease Response CRF. An overall disease response of "NE" shall be considered a valid post-baseline response for this purpose. Death or clinical progression without imaging documented in the End of Study form may also be considered a valid post-baseline response. The Efficacy Population will be used for all efficacy analyses.

11.5 Screened Population

The Screened Population is defined as all patients who sign an informed consent for the study. Screen failure patients and disposition summaries will be displayed using the Screened Population.

12.0 Interim Analyses

No interim analyses are planned for this study.

13.0 Statistical Methods

Unless otherwise stated, data from 3 cohorts will be analyzed and reported separately by cohort.

Categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts. Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the mean, median, Q1, and Q3 to a further decimal place and the SD to two additional decimal places.

Missing data will not be imputed other than the circumstances mentioned in Section 10.4.

For summary tables of efficacy endpoints where point estimates cannot be computed, the value "NA" will be reported. For summary tables of efficacy endpoints where confidence intervals cannot be computed, the value "(NA, NA)" will be reported.

All analyses will use SAS version 9.4 or higher.

13.1 Subject Disposition

The number and percentage of subjects screened, enrolled, and treated in the study will be presented, together with the number and percentage of subjects who discontinue VE800, Nivolumab or leave the study prematurely and a breakdown of the corresponding reason for discontinuation.

Tabulations of the number and percentage of subjects included in each analysis set, together with a breakdown of the reason for exclusion for non-evaluable subjects will be provided.

A tabulation of the number and percentage of subjects, enrolled, and treated with VE800 and nivolumab at each center will be presented.

Patient eligibility, and enrollment status will be listed. Subjects who discontinued VE800, Nivolumab or withdrew from the study will be listed.

13.2 Important Protocol Deviations

The study specific Protocol Deviation Guidance Document defines all important protocol deviations.

[redacted]

13.3 Treatments

13.3.1 Extent of Study Drug Exposure

Exposure to VE800 and nivolumab will be summarized in the safety analysis set. Vancomycin compliance (yes or no) will be summarized in the baseline characteristics table.

For VE800, the summary will include the duration of exposure (weeks), cumulative dose administered (capsules), subjects with at least 1 dose not administered, and absolute and relative dose intensities.

For nivolumab, the summary will include the duration of exposure (cycles), total number of actual infusions administered, cumulative dose administered (mg), subjects with at least 1 dose not administered, subjects with at least 1 dose interruption, and relative dose intensity.
Exposure to VE800 and nivolumab will also be listed.

[redacted]

[redacted]

13.3.2 Prior and Concomitant Medications

All medications and supplements administered within 14 days prior to screening through the last follow-up visit will be recorded in a log electronic case report form (eCRF) page. All antibiotics used within the 60 days prior to Screening will be recorded in the eCRF. Medications are considered prior medications if they have a start date prior to the date of first dose of study medication (VE800 or nivolumab). Concomitant medications are defined as medications administered to study participants on or after the first dose of study treatment (VE800 or nivolumab). A medication can be considered both prior and concomitant.

Prior and concomitant medications will be coded using the World Health Organization (WHO) medical dictionary (September 2019 or higher). For the purpose of categorizing prior versus concomitant medications, partially or completely missing start dates and end dates will be imputed via the rules in Section 10.4.

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary. Prior and concomitant medications will be summarized in two separate tables and categorized by Anatomical Therapeutic Chemical (ATC) Classification. Listings will be created for prior and concomitant medications.

13.3.3 Systemic Anti-Cancer Therapy Regimen and Radiation Procedures

Prior and concomitant systemic anti-cancer therapy regimen will be coded using WHO Drug Dictionary (September 2019 or higher). Concomitant systemic anti-cancer therapies and radiotherapy will be summarized and listed, including regimen number, ATC medication name/PT/verbatim term, start date (day)/stop date (day), type of therapy, therapy setting, best response and date of best response, best response and date of best response for immune checkpoint inhibitor (iCPI) therapy (for melanoma only), and date of progressive disease.

13.4 Demographic and Baseline Characteristics

Baseline demographic characteristics variables will be summarized in the full analysis set.

The summary will include age (years), sex, ethnicity, race, weight (kg), height (cm), Eastern Cooperative Oncology Group (ECOG) status, temperature, systolic blood pressure, diastolic blood pressure, pulse and vancomycin compliance (yes or no).

[redacted]

[redacted]

Listing of the demographic and baseline characteristics will also be presented.

13.5 Disease History and Characteristics

The history and characteristics of the disease under study at first diagnosis and at screening will be summarized and listed by cohort. The variables include time from first diagnosis to screening (months), stage, metastatic status and histological classification at first diagnosis, grade, stage, metastatic status and histological classification at screening, microsatellite stability status, and PD-L1 expression. Time from diagnosis to screening (months) is defined as (date of screening – date of initial diagnosis + 1) / 30.4375.

13.6 Medical History

Medical history will be tabulated by system organ class and coded using MedDRA version 22.1 or higher and preferred term using counts and percentages for the full analysis set. Medical history will be also listed.

13.7 Efficacy Analyses

The primary efficacy endpoint is the ORR, defined as the proportion of patients achieving a best overall response of CR or PR from C1/D1 until disease progression or start of a new anti-cancer therapy, whichever comes first. Objective responses will be confirmed no less than 4 weeks after the criteria for response are met.

Secondary efficacy endpoints include Antitumor response based on change in measurable tumor burden, DOR, BOR, DCR, PFS and OS. All response assessments in this section will follow RECIST 1.1. DCR is defined as the percentage of patients who have achieved CR, PR or stable disease (SD). Change in measurable tumor burden at will be calculated for each assessment time point. Landmark PFS at 6 and 12 months will be evaluated.

[redacted]

All efficacy endpoints will be summarized on the data from patients by tumor cohort. The primary efficacy analysis is based on the Efficacy Population. All analyses will include summary statistics, including number of patients (n) and percentage (%) for categorical variables and number of patients, mean, standard

deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using Kaplan-Meier (KM) methods.

The date of response or progression will be the Date of Procedure recorded for the tumor assessment for each applicable time point.

[redacted]

13.7.2 Primary Endpoint

ORR is defined as the number of patients with ORR divided by the number of patients in the efficacy population. ORR will be categorized in accordance with RECIST 1.1 and is defined as having a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR). BOR is defined as the best response among all overall responses (in the order CR, PR, stable disease [SD], progressive disease [PD], and not evaluated [NE]) recorded from C1/D1 until disease progression or start of new anti-cancer therapy, whichever comes first. Confirmation of CR or PR should be at least 4 weeks between previous tumor assessment/imaging and confirmation. If the status of CR or PR cannot be confirmed by repeat tumor assessment, the BOR of unconfirmed CR and PR will be determined per RECIST 1.1. The status of BOR of SD requires the SD assessment to be more than 4 weeks from baseline. Patients without a valid clinical response assessment will be assigned a BOR of NE.

The number and percentage of patients with OR, DCR, and each category of BOR (CR, PR, SD, PD, NE) and DCR (percentage of patients who have achieved CR, PR, or SD) will be presented by cohort along with the 90% CI using the Clopper-Pearson method. Listings of tumor assessments and responses assessment will be provided. Spider plots will be produced to depict each patient's percentage change in tumor size as a line over time. Waterfall plots will present each patient's best percentage change in tumor size as a separate bar, with the bars ordered from the largest increase to the largest decrease.

13.7.3 Secondary Endpoints

13.7.3.1 Best Overall Response and Disease Control Rate

BOR and DCR will be included in the analysis of ORR (Section 13.7.2)

13.7.3.2 Duration of Response

DOR (in months) is defined for patients with confirmed CR or confirmed PR, i.e. responders, as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of PD or death due to any cause, whichever is earlier. DOR (in months) is calculated as (event or censor date – first objective response date + 1) / 30.4375. Patients who have not progressed or died at the time of analysis will be censored at the latest date of response assessment with a CR, PR, or SD. However, if the patient progresses or dies after two or more consecutive missed scheduled visits, the patient will be censored at the latest date of response assessment with a CR, PR, or SD.

For each cohort, an event/censoring summary, Kaplan-Meier plots, and Kaplan-Meier quartile estimates (with 90% CIs) will be provided.

13.7.3.3 Progression-Free Survival

Progression-free survival (PFS) is defined as time from C1/D1 to progression or death due to any cause, whichever occurs earlier. PFS (in months) is calculated as (death or censor date – date of C1/D1 + 1) / 30.4375. Patients who have not progressed or died at the time of analysis will be censored at the latest date of response assessment with a CR, PR, or SD. However, if the patient progresses or dies after two or more consecutive missed scheduled visits, the patient will be censored at the latest date of response assessment with a CR, PR, or SD. Patients who have not died or who died after end of study and have no evaluable response assessment (CR, PR, or SD) or do not have a baseline assessment will be censored at C1/D1.

For each cohort, an event/censoring summary, Kaplan-Meier plots, Kaplan-Meier quartile estimates (with 90% CIs), and Kaplan-Meier estimates (with 90% CIs) at 6- and 12-month landmarks will be provided.

13.7.3.4 Overall Survival

Overall survival (OS) is defined as time from C1/D1 to death due to any cause. OS (in months) is calculated as (death or censor date – date of C1/D1 + 1) / 30.4375. For patients alive, censoring for survival will be done on the date of the last on study follow-up that the patient is reported to be alive.

For each cohort, an event/censoring summary, Kaplan-Meier plots, Kaplan-Meier quartile estimates (with 90% CIs), and Kaplan-Meier estimates (with 90% CIs) at 6- and 12-month landmarks will be provided.

13.8 Safety Analyses

13.8.1 Adverse Events

Treatment-emergent adverse events (TEAE) are defined in Section 10.3. Only TEAE will be included in this section unless otherwise mentioned. All AE will be coded according to the MedDRA Version 21.0 or higher dictionary by system organ class (SOC), preferred term (PT), and severity grade using NCI CTCAE v. 5.0.

All adverse event summary tables will be based on the Safety Population.

A breakdown of the number and percentage of subjects reporting each TEAE, categorized by SOC and PT coded according to the MedDRA dictionary, will be presented. Note that counting will be by subject and not by event and subjects are only counted once within each SOC or PT. Relationships to either VE800 or nivolumab are categorized as related, possibly related, unlikely related or as recorded on the CRF. [redacted]

TEAE will be presented by PT in descending order of frequency. A further summary of the number and percentage of patients reporting each adverse event in at least 5% of patients in the Safety population as well as summary of adverse events reported categorized by CTCAE grade will be presented by PT in descending order of frequency.

All AEs (including non-treatment-emergent events) recorded on the CRF will be listed using the Enrolled Population.

13.8.2 Deaths and Serious Adverse Events

SAEs are a subset of collected AEs with a Yes to the question of “Was the adverse event serious?” in the Adverse Event Form in CRF.

TEAEs that lead to death and SAEs will be summarized by SOC and PT. The following summaries will be presented:

- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Serious Treatment-related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term
- Serious VE800-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Serious Nivolumab-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Serious Vancomycin-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Treatment-related Treatment-Emergent Adverse Events with an Outcome of Death by System Organ Class and Preferred Term
- VE800-related Treatment-Emergent Adverse Events with an Outcome of Death by System Organ Class and Preferred Term

- Nivolumab-related Treatment-Emergent Adverse Events with an Outcome of Death by System Organ Class and Preferred Term

[redacted]

[redacted]

13.8.5 Laboratory Data

Table 1 lists all laboratory assessments and they will be done by local laboratories. All laboratory data will be summarized in International System (SI) units. In general, laboratory data will be presented by scheduled visits. Values at unscheduled visits will be included in the summary of maximum for all visits and minimum for all visits, which will present the largest and smallest post-baseline values observed for each patient for each test.

Selected parameters will be presented in shift tables of baseline against maximum grade (NCI CTCAE v. 5.0) test result. The shift from baseline to maximum post baseline (including unscheduled visit) will be presented by cohort for AST (AST increased), ALT (ALT increased), bilirubin (bilirubin increased), creatinine (creatinine increased), sodium (hyponatremia and hypernatremia), potassium (hypokalemia and hyperkalemia), calcium (hypocalcemia and hypercalcemia).

For sodium, potassium, and calcium, separate grading criteria exist depending whether the analyte is high or low. For shift tables, all low values will be included in the Grade 0 group in the shift tables for high values, and vice versa (all high values should be included in the Grade 0 group in the shift tables for low values).

Patients with at least 1 on-study measurement for each laboratory parameter will be included, regardless of whether a baseline assessment is present.

Clinical laboratory results, including unscheduled visits, will be listed by subject.

Table 1 Laboratory Tests in the Study

Category	Parameter
Hematology	Hemoglobin
	Hematocrit
	Total leukocyte count, including differential
	Platelet count
Coagulation - at screening only, or if clinically indicated	Prothrombin time (PT)/international normalized ratio (INR)
	Activated partial thromboplastin time (aPTT)
Chemistry	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Amylase
	Alkaline phosphatase (ALP)
	Total bilirubin
	Albumin - screening only
	Sodium

	Potassium
	Lactate dehydrogenase (LDH)
	Lipase
	Creatinine
	Blood urea nitrogen (BUN) or serum urea
	Fasting glucose - at screening only, or if clinically indicated
	Chloride
	Calcium
	Phosphorus
Thyroid Panel	Thyroid stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) – at screening only, or if clinically indicated
Urinalysis	pH
	Specific gravity
	Turbidity
	Color
	Protein
	Occult blood
	Ketones
	Glucose
	Bilirubin
	Nitrite
	Urobilinogen
	Leukocyte esterase
Serology	Hepatitis B/C, (HBsAG, anti-HCV, or HCV RNA) – at screening only, or if clinically indicated
	HIV testing (where mandated locally)
Other Analyses	Pregnancy test (women of childbearing potential only: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG])
	Follicle stimulating hormone (FSH) screening (only required to confirm menopause in women <55 years of age)

13.8.5.1 Hematology

Hematology parameters include CBC, hemoglobin, hematocrit, neutrophil count, lymphocyte count, and platelet count.

Descriptive statistics will be provided for each test result and for change from baseline by scheduled visit. Multiple measurements taken during the visit for a patient will be represented by the most severe value for each hematology test. The most severe value will be determined first by the value closest to the upper or lower limit of the normal limits (dependent on which direction is considered severe) if the value is within the normal limits. If the value is outside the normal limits, the value furthest from the upper or lower limit will be selected (dependent on which direction is considered severe). If this algorithm does not allow for determining the most severe (e.g. a tie, etc.) the first chronological value will be selected. Low values are considered the most severe for all hematology parameters. Hematology results for each patient and patients who develop a ≥Grade 3 toxicity will be listed.

13.8.5.2 Chemistry

Descriptive statistics will be provided for each test result and for change from baseline by scheduled visit. Multiple measurements taken during the visit for a patient will be represented by the most severe value as noted in Section 13.8.5.1. For all chemistry analytes, the most severe value is the highest value, except for albumin, and chloride. The most severe could be in either direction for potassium, sodium, and calcium. For these analytes, if within the normal limits, then the value closest to the normal limit (either direction) will

be selected. If outside the normal limits, then the value most distant from the normal limit (either direction) will be used. Chemistry results for each patient and patients who develop a ≥Grade 3 toxicity will be listed.

13.8.5.3 Urinalysis

Results and change from baseline by scheduled visit will be summarized for pH and specific gravity. For other parameters, including turbidity, color, protein, occult blood, ketones, glucose, bilirubin, nitrite, urobilinogen, and leukocyte esterase, their results will be categorized as normal, abnormal but not clinically significant, abnormal and clinically significant and summarized by scheduled visit. Urinalysis results for each patient and patients who develop a ≥Grade 3 toxicity will be listed.

13.8.5.4 CTCAE Coding of Laboratory Data

Where laboratory values are categorized into NCI CTCAE v5.0, the categories are defined according to the criteria available on the following website: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Note that grades are applied based only on the numeric SI value of the parameter assessed; clinical signs and symptoms are not considered. Where categories are only distinguished by clinical signs or symptoms, the lowest of the possible grades will be assigned.

Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as “Grade 0,” which is defined as normal.

13.8.6 Vital Signs and ECOG Performance Status

The vital signs collected on this study are height (m, at screening only), weight (kg), body temperature (°C), systolic and diastolic blood pressure (mmHg), and pulse (beats/min). These are entered on the Vital Signs CRFs. The Eastern Cooperative Oncology Group (ECOG) performance status will be entered on the ECOG Performance Status Questionnaire at screening, Day 1 of every cycle, and at end of treatment (EOT). ECOG performance will be graded according to the ECOG Scale of Performance Status:

Table 2: ECOG Scale of Performance Status

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

Vital signs and their change from baseline will be summarized by scheduled visits and by cohort. Summaries will include the maximum and minimum post-baseline values observed and change from baseline to that observed value.

ECOG performance status will be listed for all visits and summarized at baseline and scheduled visits.

All vital signs and ECOG performance status will be listed.

13.8.7 Physical Examinations

Results of physical examinations of body systems (normal/abnormal) are captured on the Physical Examinations CRF. Physical examinations will be summarized by scheduled visits and by body system. Physical examination data will also be listed.

13.8.8 ECGs

Single 12-lead ECGs will be performed and heart-rate corrected QT interval using Fridericia's formula (QTcF) will be collected. Post-baseline abnormal ECG measurements will be recorded as AEs if they are reported as clinically significant by the Investigator.

A summary of QTcF (msec) and change from baseline will be presented for each planned visit as well as the minimum, maximum . A shift from baseline to maximum CTCAE grade summary will also be presented.

A summary of maximum QTcF and maximum change from baseline will be generated following the ICH E14 Category. Categories for maximum QTcF include ≤ 450 msec, > 450 to ≤ 480 msec, > 480 to ≤ 500 msec, and > 500 msec. Categories of maximum change include ≤ 30 msec, > 30 to ≤ 60 msec, and > 60 msec. A separate listing of the ECG results along with the overall interpretation will be presented.

13.8.9 Important Protocol Deviation Identification Listings

Potential planned or unplanned protocol deviations noted during clinical monitoring will be documented by category (i.e., inclusion criteria, exclusion criteria, study drug administration, study procedures and assessments, study visit schedule, informed consent, and other). All deviations will be reviewed, categorized, designated important or not important, and finalized prior to database lock. Important protocol deviations will be defined as those potentially impacting safety or efficacy assessments. Additional details of what will be considered important can be found in the Protocol Deviation Guidance document.

13.8.10 Long Term Follow-up

Long term follow-up/survival data will be listed for the safety population. Additionally, all follow-up disease recurrence will be listed.

13.8.11 Death Report

Death report data will be summarized and listed for the Enrolled Population.

14.0 References

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. *5*, 649-655.
OPDIVO (nivolumab) injection for intravenous use [package insert]. Princeton (NJ): Bristol-Myers Squibb. (March 2019). Retrieved from https://packageinserts.bms.com/pi/pi_opdivo.pdf.

OPDIVO Summary of Product Characteristics. (2018). Retrieved from https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf.
Pardoll, D. (2003). Does the immune system see tumors as foreign or self? *Annu Rev Immunol*. *21*, 807-839.

[redacted]

US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. (27 November 2017). Retrieved from https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

Wolchok, J.D., Hoos, A., O'Day, S., Weber, J.S., Hamid, O., Lebbè, C., et al. (2009). Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. *15*, 7412-7420.

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

[redacted]

15.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BOR	Best overall response
BUN	Blood urea nitrogen
CBC	Complete blood count
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
C1/D1	Cycle 1, Day 1
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
FSH	Follicle stimulating hormone
fT3	Free triiodothyronine
fT4	Free thyroxine
GEJ	Gastroesophageal Junction
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
iCPI	Immune checkpoint inhibitor
INR	International normalized ratio
[redacted]	[redacted]
IV	Intravenously

LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MSS	Microsatellite-stable
NCI	National Cancer Institute
NE	Not evaluable
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PT	Prothrombin time
QD	Once per day
QID	Four times per day
QTcF	Heart-rate corrected QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAP	Statistical analysis plan
SAE	Serious adverse event
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
WHO	World Health Organization