Official Title of Study:

A Phase 3, Randomized, Double-blind Study of BMS-986205 Combined with Nivolumab versus Nivolumab in Participants with Metastatic or Unresectable Melanoma that is Previously Untreated

NCT Number: NCT03329846

Document Date (Date in which document was last revised): July 23, 2020

STATISTICAL ANALYSIS PLAN
FOR SYNOPTIC CLINICAL STUDY REPORT

A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY OF BMS-986205 COMBINED WITH NIVOLUMAB VERSUS NIVOLUMAB IN PARTICIPANTS WITH METASTATIC OR UNRESECTABLE MELANOMA THAT IS PREVIOUSLY UNTREATED

PROTOCOL(S) CA017055

VERSION # 1.0

TABLE OF CONTENTS

LIST OF FIGURES

[redacted]

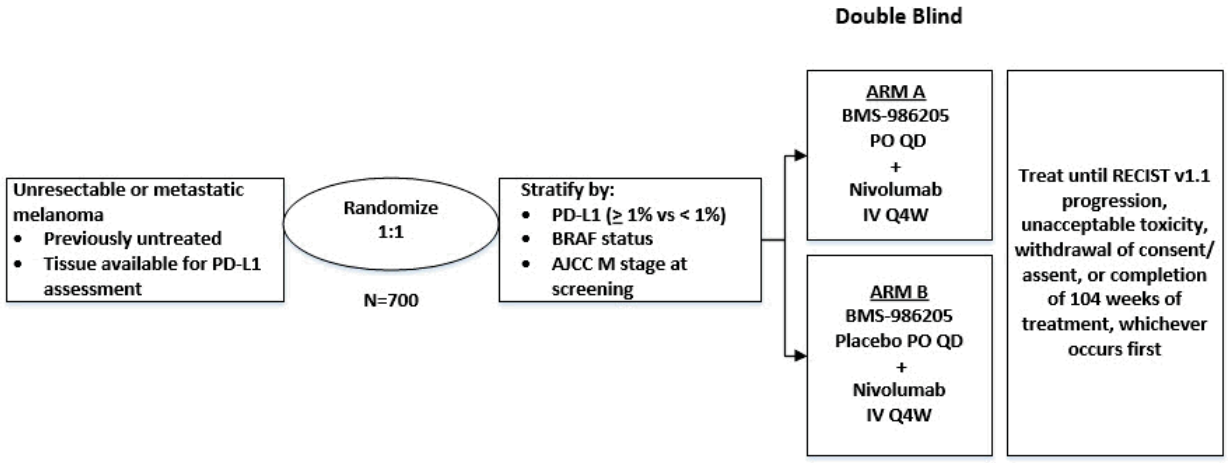
2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 3, randomized, double-blind study of BMS-986205 in combination with nivolumab versus nivolumab in combination with BMS-986205 placebo in adult (18 years of age and older, or age of majority) and adolescent (≥ 12 years of age, where locally acceptable; otherwise ≥ 18 years of age) participants with unresectable or metastatic melanoma that is previously untreated. This study is double-blinded with respect to BMS-986205; BMS-986205 Placebo PO QD will be administered in combination with nivolumab administered IV Q4W in the nivolumab monotherapy arm. Participants must have unresectable Stage III or Stage IV melanoma, per the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual[2], and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant therapy in participants with previously completely resected disease that has now recurred is permitted if this therapy was completed at least 6 months prior to randomization.

The study design schematic in adults and adolescents is presented in Figure 2.1-1.

Figure 2.1-1: Study Design Schematic



A pre-treatment tumor sample to determine PD-L1 status is required to be submitted from all participants prior to randomization. The sample must be obtained within 3 months prior to enrollment from a metastatic tumor lesion or from an unresectable primary tumor lesion. The tumor sample must be taken from a site of disease which has not been previously irradiated. In addition, no intervening treatment may have been administered between the time of biopsy/surgery and randomization. Pre-treatment tumor tissue biopsy specimens in the form of a paraffin-embedded block or, optimally, at least 20 unstained slides, will be requested; a minimum of 10 slides is required. The pre-treatment tumor sample must be a core biopsy, punch biopsy, excisional

biopsy, or surgical specimen; fine needle aspiration samples and cytology samples are not acceptable. If sufficient tissue is not available from within 3 months prior to enrollment, then a fresh biopsy will be required during the screening period. Samples will be submitted to the analytical laboratory for PD-L1 testing. The analytical laboratory must provide IRT with confirmation of the related results prior to randomization.

Participants must have a documented *BRAF* mutational status prior to randomization. Those participants enrolling in this study without known results must have testing performed locally and results (wild type or mutant) be available prior to randomization. Participants with indeterminate or unknown *BRAF* mutational status results will not be permitted to be randomized in the study.

During the treatment phase, participants will receive:

- Arm A: BMS-986205 100 mg PO QD and Nivolumab 480 mg IV Q4W for up to 104 weeks (approximately 2 years)
- Arm B: BMS-986205 Placebo PO QD and Nivolumab 480 mg IV Q4W for up to 104 weeks (approximately 2 years)

Dose reductions will be not be allowed for nivolumab; dose reductions will be permitted for double-blind BMS-986205 (or matching placebo) if the participant is an adult or an adolescent receiving 100mg tablets. No dose reductions for BMS-986205 (or matching placebo) will be allowed for adolescent participants receiving 50 mg tablets.

Treatment beyond initial investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined progression is permitted if the participant has investigator-assessed clinical benefit, is tolerating study treatment, and has not yet completed 104 weeks of study treatment.

2.2 Treatment Assignment

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by calling an IRT to obtain the participant number. Every participant who signs the informed consent form must be assigned a participant number in IRT. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Year of birth
- Gender at birth

Once enrolled in IRT, enrolled participants who have met all eligibility criteria will be ready to be randomized through the IRT. The following information is required for participant randomization:

- Participant number

- Year of birth
- PD-L1 status (PD-L1 positive vs. PD-L1 negative/indeterminate) entered by vendor
- BRAF V600 mutational status
- M (Metastatic) Stage at screening

Participants meeting all eligibility criteria will be randomized in a 1:1 ratio and stratified by PD-L1 status, BRAF status, and AJCC M stage as described below:

- PD-L1 status
  - PD-L1 positive (≥ 1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells) vs.
  - PD-L1 negative (< 1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells) / indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)
- *BRAF* mutational status
  - BRAF V600 mutation positive vs.
  - BRAF V600 wild type
- AJCC M stage at screening
  - M0/M1a(0)/M1b(0) vs.
  - M1a(1)/M1b(1)/M1c(any)/M1d(any)

The randomization procedures will be carried out via permuted blocks within each stratum, defined by combination of PD-L1 status (positive, negative/indeterminate), BRAF V600 mutational status (BRAF mutated, BRAF wild type), and M Stage (M0/M1a(0)/M1b(0), M1a(1)/M1b(1)/M1c(any)/M1d[any]). The exact procedures for using the IRT will be detailed in the IRT manual.

2.3 Blinding and Unblinding

Treatment allocation will be unblinded upon approval of Revised Protocol 01 and a list of treatment assignments for each subject will be provided to each site with randomized subjects.

2.4 Protocol Amendments

Revised Protocol 01 on 13-Jun-2018.

2.5 Data Monitoring Committee

NA.

3 OBJECTIVES

Not applicable per Revised Protocol 01.

3.1.1 Safety

Safety will be analyzed through the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose modification, and specific laboratory abnormalities (worst grade) in each treatment arm. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

4 ENDPOINTS

[redacted]

5 SAMPLE SIZE AND POWER

NA.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment. Evaluations on the same date and time of the first dose of study treatment will be considered as baseline evaluations. For subjects who are randomized but not treated, baseline evaluation will be defined as those that occur before the date and time of randomization.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- 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
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline.

6.1.2 Post Baseline Period

On-treatment AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). An AE will be counted as on-treatment if the event occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

On-treatment evaluations (laboratory tests, pulse oximetry, and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study

treatment. An evaluation will be counted as on-treatment if it occurred within a safety window of 30 days (or 100 days depending on analysis) of the last dose of study treatment.

Late emergent drug-related AEs will be defined as drug-related AEs with an onset date greater than 100 days after the last dose of study treatment in subjects who are off study treatment.

6.2 Treatment Regimens

The treatment group "**as randomized"** will be retrieved from the IRT system.

- Arm A: BMS-986205 100 mg PO QD and Nivolumab 480mg IV Q4W
- Arm B: BMS-986205 Placebo PO QD and Nivolumab 480mg IV Q4W

The treatment group "**as treated**" will be the same as the arm as randomized by IRT. However, if a participant received the incorrect drug for **the entire period** of treatment, the participant's treatment group will be defined as the incorrect drug the participant actually received.

6.3 Populations for Analyses

- Enrolled participants: All participants who signed informed consent and were registered into IRT.
- All treated participants: All participants who received at least one dose of any study medication, including placebo doses.
- All randomized participants: All participants who are randomized to any treatment group.
- PK: All randomized participants with available serum time-concentration data.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category, grouped by treatment (with total). Percentages given in these tables will be rounded and, therefore, may not always sum to 100%.

Continuous variables will be summarized by treatment group (with total, as needed) using the mean, standard deviation, median, quartiles, minimum and maximum values, unless specified otherwise.

7.2 Study Conduct

7.2.1 Participant Disposition

Pre-Randomized (Before Double-blind Period) Subject Status and Subject Status on treatment will be summarized. A participant listing for all randomized participants will be provided showing the participant's randomization date, first and last dosing date, off treatment date and reason for going off-study treatment. Information regarding off-study reason will be included if available.

7.2.2 Demographic and Baseline Characteristics

Listings will be provided for demographic characteristics (including age, race and gender) for all treated participant.

7.2.3 Medical History

Not applicable (not required for a synoptic CSR)

7.2.4 Prior Therapy

Not applicable (not required for a synoptic CSR)

7.3 Extent of Exposure

A listing of study medication received will be provided for all treated participants.

[redacted]

7.3.2 Subsequent Anti-Cancer Therapy

Not applicable (not required for a synoptic CSR)

[redacted]

7.5 Safety

The safety analysis will be presented in all treated participants, unless otherwise specified.

7.5.1 Deaths

A list of death will be provided for all enrolled participants.

7.5.2 Serious Adverse Events

Serious adverse events will be summarized by treatment group:

- Overall summary of SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

All analyses will be conducted using the 30-day safety window.

A by-subject SAE listing will be provided for the “enrolled subjects” population.

7.5.3 Adverse Events Leading to Discontinuation of Study Therapy

A list of adverse events leading to discontinuation of study therapy will be provided for all treated participants.

7.5.4 Adverse Events

Adverse events will be summarized by treatment group.

The following analyses will be conducted using the 30 days safety window:

- Overall summary of any AEs by worst CTC grade (1, 2, 3, 4, 5, not reported, total) presented by SOC/PT.
- Overall summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

A by-subject AE listing will be provided.

7.5.5 Laboratory Parameters

Laboratory parameters including hematology, serum chemistry, liver function, and renal function in SI units will be summarized using worst grade by treatment group for all treated participants.

A by-subject listing of these laboratory parameters will be provided.

[redacted]

9 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[3].

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive.
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive.

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

* In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions may be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g., time from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

10 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

[redacted]