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PHASE IIIB, RANDOMIZED STUDY OF MULTIPLE ADMINISTRATION REGIMENS FOR NIVOLUMAB PLUS IPILIMUMAB IN SUBJECTS WITH PREVIOUSLY UNTREATED UNRESECTABLE OR METASTATIC MELANOMA

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

PHASE IIIB, RANDOMIZED, STUDY OF MULTIPLE ADMINISTRATION REGIMENS
FOR NIVOLUMAB PLUS IPILIMUMAB IN SUBJECTS WITH PREVIOUSLY
UNTREATED UNRESECTABLE OR METASTATIC MELANOMA

PROTOCOL(S) CA209742

VERSION # 2.0
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Research Hypothesis:
Treatment with BMS-986214 will demonstrate no clinically relevant differences in safety relative to nivolumab and ipilimumab administered sequentially in patients with previously untreated, unresectable, or metastatic melanoma.

Schedule of Analyses:
The incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period is the primary endpoint for this study. The first (primary) analysis will be carried out for primary endpoint, safety-related secondary, and PK-related secondary endpoints when all participants who are still on-treatment complete the Part 1 period. The final analysis will be carried out for efficacy-related secondary endpoints when all patients have at least 9 months of follow-up. Safety-related exploratory endpoints will also be analyzed at the time of both first (primary) analysis and final analysis. Efficacy-related exploratory endpoints will be analyzed at the time of the final analysis if data are available.

The duration of the study
- from start of randomization to primary analysis of the study is expected to be approximately 10 months (7 months of accrual plus approximately an additional 3 months to ensure all subjects who are still on-treatment have completed the Part 1 period)
- from start of randomization to final analysis of the study is expected to be approximately 16 months (7 months of accrual plus an additional 9 months to ensure all patients have at least 9 months of follow-up).

Subsequent descriptive analyses may be performed to summarize additional safety and survival data and to incorporate tumor assessment data captured beyond the primary and secondary endpoint analyses. Additional survival analysis may be conducted for up to 5 years beyond analysis of the primary endpoint.

2 STUDY DESCRIPTION

2.1 Study Design
This is a Phase IIIb, open-label, randomized 2-arm study of the Fixed Ratio Combination product (BMS-986214).

In Arm A, BMS-986214 will be administered as one 60 minute infusion. Subjects will receive a total of four doses in Part 1.
In Arm B, nivolumab and ipilimumab will be administered sequentially, as two separate infusions, one 60 minute nivolumab infusion and one 90 minute ipilimumab infusion with a 30 minute break between each infusion.

Six weeks after the administration of the last combination dose in Part 1, subjects will then receive nivolumab flat dose (480 mg, 30 minute infusion) every four weeks in Part 2 until progression or unacceptable toxicity (total maximum treatment duration up to 2 years including Part 1 and Part 2).

Safety of subjects will be monitored on an ongoing basis by the study team. The BMS medical monitor is a physician who is responsible for reviewing the safety of patients in this study in a systematic and continuous manner. This includes a review of serious and non-serious adverse events including all hematological and non-hematological events.

In addition, study safety is evaluated on an ongoing basis by representatives of BMS Global Pharmacovigilance and the BMS medical safety team (MST), who operate independently from the clinical team and monitor safety across all nivolumab protocols, identify potential safety signals, notify appropriate stakeholders of relevant findings, and implement risk management plans.

The study population for this trial will include male and female patients ≥ 15 years of age (except where local regulations and/or institutional policies do not allow for subjects < 18 years of age (pediatric population) to participate. Preliminary analysis of a pediatric nivolumab study also indicated that nivolumab exposure (observed trough concentrations after the 1st dose) was similar between pediatric (age 6 to 12 yr) and adult patients. For those sites, the eligible subject population is ≥ 18 years) with previously untreated, unresectable or metastatic melanoma. Subjects must have unresectable or metastatic Stage III or Stage IV melanoma, as per the AJCC staging system and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma.

Subjects who advance to Part 2 will be treated until progression or unacceptable toxicity (total maximum treatment duration up to 2 years including Part 1 and Part 2).

The study design schematic is presented in Figure 2.1-1.
2.2 Treatment Assignment

After the subject’s initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by accessing an Interactive Response Technologies web-based system (IRT) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IRT. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

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

- Subject number
- Date of birth
- PD-L1 expression level (PD-L1 ≥ 5% expression vs PD-L1 < 5% expression/indeterminate) entered by vendor
- M Stage at screening (M0/M1a/M1b vs. M1c) (See Appendix 4 of the protocol)
Subjects meeting all eligibility criteria will randomize 1:1 ratio to Arm A or Arm B and stratified by the following factors:
- PD-L1 expression (PD-L1 ≥ 5% expression vs PD-L1 < 5% expression/indeterminate)
- M stage(M0/M1a/M1b vs. M1c)

The randomization procedures will be carried out via permuted blocks within each stratum.

**2.3 Blinding and Unblinding**

This is an open-label study.

**2.4 Protocol Amendments**

This SAP incorporates the following amendments:

<table>
<thead>
<tr>
<th>Table 2.4-1: Protocol Amendments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment</td>
</tr>
<tr>
<td>Revised Protocol 01</td>
</tr>
</tbody>
</table>

**3 OBJECTIVES**

**3.1 Primary**

The primary objective is to evaluate the difference in safety between co-administered FRC nivolumab 1 mg/kg and ipilimumab 3 mg/kg relative to sequentially administered nivolumab 1 mg/kg and ipilimumab 3 mg/kg as measured by the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period in subjects with previously untreated, unresectable or metastatic melanoma.
3.2 Secondary

- To evaluate incidence of AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ and the select AE hypersensitivity/infusion reaction category
- To evaluate Grade 3 - 5 AE incidence rate (drug-related and all causality) defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria
- To determine PK comparisons of nivolumab and ipilimumab administered as FRC to that of sequentially administered nivolumab and ipilimumab
- To evaluate the objective response rate (ORR), as determined by investigators
- To evaluate progression free survival (PFS)

4 ENDPOINTS

4.1 Primary Endpoint: MedDRA Anaphylactic Reaction Broad Scope SMQ AE Incidence Rate

The primary endpoint of the study is the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period. This incidence rate is defined as number of subjects who experienced at least 1 AE in the MedDRA Anaphylactic Reaction broad scope SMQ with onset on the day of or within 2 days after any study therapy infusion during the combination period (Part 1) divided by number of treated subjects. For reference, the terms currently included in the MedDRA Anaphylactic Reaction SMQ based on MedDRA version 19.0 are listed in Table 4.1-1.
The analysis of the primary endpoint will occur when all treated subjects who are still on-treatment complete the Part 1 period.
<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Term Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory failure</td>
<td>Broad</td>
</tr>
<tr>
<td>Allergic oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Narrow</td>
</tr>
<tr>
<td>Anaphylactic shock</td>
<td>Narrow</td>
</tr>
<tr>
<td>Anaphylactic transfusion reaction</td>
<td>Narrow</td>
</tr>
<tr>
<td>Anaphylactoid reaction</td>
<td>Narrow</td>
</tr>
<tr>
<td>Anaphylactoid shock</td>
<td>Narrow</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Asthma</td>
<td>Broad</td>
</tr>
<tr>
<td>Blood pressure decreased</td>
<td>Broad</td>
</tr>
<tr>
<td>Blood pressure diastolic decreased</td>
<td>Broad</td>
</tr>
<tr>
<td>Blood pressure systolic decreased</td>
<td>Broad</td>
</tr>
<tr>
<td>Bronchial oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Broad</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>Broad</td>
</tr>
<tr>
<td>Cardio-respiratory arrest</td>
<td>Broad</td>
</tr>
<tr>
<td>Cardio-respiratory distress</td>
<td>Broad</td>
</tr>
<tr>
<td>Cardiovascular insufficiency</td>
<td>Broad</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>Broad</td>
</tr>
<tr>
<td>Choking</td>
<td>Broad</td>
</tr>
<tr>
<td>Choking sensation</td>
<td>Broad</td>
</tr>
<tr>
<td>Circulatory collapse</td>
<td>Narrow</td>
</tr>
<tr>
<td>Circumoral oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Cough</td>
<td>Broad</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Broad</td>
</tr>
<tr>
<td>Dialysis membrane reaction</td>
<td>Narrow</td>
</tr>
<tr>
<td>Diastolic hypotension</td>
<td>Broad</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Broad</td>
</tr>
<tr>
<td>Erythema</td>
<td>Broad</td>
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<tr>
<td>Eye oedema</td>
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</tr>
<tr>
<td>Eye pruritus</td>
<td>Broad</td>
</tr>
<tr>
<td>Eye swelling</td>
<td>Broad</td>
</tr>
<tr>
<td>Eyelid oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Face oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Flushing</td>
<td>Broad</td>
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</table>
Table 4.1-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

<table>
<thead>
<tr>
<th>Preferred Term (^a)</th>
<th>Term Scope (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised erythema</td>
<td>Broad</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>Broad</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Broad</td>
</tr>
<tr>
<td>Injection site urticaria</td>
<td>Broad</td>
</tr>
<tr>
<td>Irregular breathing</td>
<td>Broad</td>
</tr>
<tr>
<td>Kounis syndrome</td>
<td>Narrow</td>
</tr>
<tr>
<td>Laryngeal dyspnoea</td>
<td>Broad</td>
</tr>
<tr>
<td>Laryngeal oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>Broad</td>
</tr>
<tr>
<td>Laryngotracheal oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Lip oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Lip swelling</td>
<td>Broad</td>
</tr>
<tr>
<td>Mouth swelling</td>
<td>Broad</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>Broad</td>
</tr>
<tr>
<td>Nodular rash</td>
<td>Broad</td>
</tr>
<tr>
<td>Ocular hyperaemia</td>
<td>Broad</td>
</tr>
<tr>
<td>Oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Oedema mouth</td>
<td>Broad</td>
</tr>
<tr>
<td>Oropharyngeal spasm</td>
<td>Broad</td>
</tr>
<tr>
<td>Oropharyngeal swelling</td>
<td>Broad</td>
</tr>
<tr>
<td>Periorbital oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Broad</td>
</tr>
<tr>
<td>Pruritus allergic</td>
<td>Broad</td>
</tr>
<tr>
<td>Pruritus generalised</td>
<td>Broad</td>
</tr>
<tr>
<td>Rash</td>
<td>Broad</td>
</tr>
<tr>
<td>Rash erythematos</td>
<td>Broad</td>
</tr>
<tr>
<td>Rash generalised</td>
<td>Broad</td>
</tr>
<tr>
<td>Rash pruritic</td>
<td>Broad</td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>Broad</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>Broad</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Broad</td>
</tr>
<tr>
<td>Reversible airways obstruction</td>
<td>Broad</td>
</tr>
<tr>
<td>Sensation of foreign body</td>
<td>Broad</td>
</tr>
<tr>
<td>Shock</td>
<td>Narrow</td>
</tr>
<tr>
<td>Shock symptom</td>
<td>Narrow</td>
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</tbody>
</table>
Table 4.1-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Term Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin swelling</td>
<td>Broad</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Broad</td>
</tr>
<tr>
<td>Stridor</td>
<td>Broad</td>
</tr>
<tr>
<td>Swelling</td>
<td>Broad</td>
</tr>
<tr>
<td>Swelling face</td>
<td>Broad</td>
</tr>
<tr>
<td>Swollen tongue</td>
<td>Broad</td>
</tr>
<tr>
<td>Tachypnoea</td>
<td>Broad</td>
</tr>
<tr>
<td>Throat tightness</td>
<td>Broad</td>
</tr>
<tr>
<td>Tongue oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Tracheal obstruction</td>
<td>Broad</td>
</tr>
<tr>
<td>Tracheal oedema</td>
<td>Broad</td>
</tr>
<tr>
<td>Type I hypersensitivity</td>
<td>Narrow</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>Broad</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Broad</td>
</tr>
<tr>
<td>Urticaria papular</td>
<td>Broad</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Broad</td>
</tr>
</tbody>
</table>

a Changes may be made to this list with each new version of MedDRA. For information, the preferred terms defined at the time of finalization of the protocol are listed using MedDRA version 19.0.

b All Narrow Scope PTs are also included in the Broad Scope.

4.2 Secondary Endpoints

The safety- and PK-related secondary endpoints will be analyzed at the time of the first (primary) analysis when all participants who are still on-treatment complete the Part 1 period. The efficacy-related secondary endpoints will be analyzed at the time of final analysis when all subjects have at least 9 months of follow-up.

4.2.1 MedDRA Anaphylactic Reaction Narrow Scope SMQ AE Incidence Rate

The first secondary endpoint is the incidence of AEs in the MedDRA Anaphylactic Reaction narrow scope SMQ occurring within 2 days after any study therapy infusion during the combination period (Part 1). This incidence rate will be defined similarly to the primary endpoint except that the event rate will be based on terms within the narrow scope SMQ rather than the broad scope.
4.2.2 Hypersensitivity/Infusion Reaction Select AE Incidence Rate

The second secondary endpoint is the incidence of events within the hypersensitivity/infusion reaction select AE category occurring within 2 days after any study therapy infusion during the combination period (Part 1). The select AEs consist of a list of preferred terms defined by the Sponsor and represent AEs with a potential immune-mediated etiology. At the time of this writing the following 5 MedDRA preferred terms are included in the hypersensitivity/infusion reaction select AE category: Anaphylactic Reaction, Anaphylactic Shock, Bronchospasm, Hypersensitivity, and Infusion Related Reaction. Changes may be made to this list with each new version of MedDRA prior to database lock. The list that is the most current at the time of analysis will be used. The incidence rate of hypersensitivity/infusion reaction select AEs will be defined similarly to the primary endpoint except that the event rate will be based on terms from the hypersensitivity/infusion reaction select AE category rather than the MedDRA Anaphylactic Reaction broad scope SMQ.

4.2.3 Drug-Related Grade 3 - 5 AE Incidence Rate

The third secondary endpoint is the drug-related Grade 3 - 5 AE incidence rate defined using NCI CTCAE version 4.0 criteria. The drug-related Grade 3 - 5 AE rate is defined as number of subjects who experienced at least 1 AE of Grade 3 or higher, judged to be related to study drug by the investigator, and with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated subjects.

4.2.4 All Causality Grade 3 - 5 AE Incidence Rate

The fourth secondary endpoint is the all causality Grade 3 - 5 AE incidence rate defined using NCI CTCAE version 4.0 criteria. The all causality Grade 3 - 5 AE rate is defined as number of subjects who experienced at least 1 AE of Grade 3 or higher with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated subjects.

4.2.5 Pharmacokinetic Analyses

The fifth secondary endpoint is PK comparisons of nivolumab and ipilimumab administered as FRC to that of sequentially administered nivolumab and ipilimumab. PK will be measured using serum concentration-time data.

4.2.6 Objective Response Rate

The sixth secondary endpoint is ORR as determined by investigators. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of treated subjects for each
treatment group. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR will be determined based on response designations up to the time of initial RECIST 1.1 progression.

4.2.7 Progression Free Survival

The seventh secondary endpoint is PFS. PFS is defined as the time from the date of randomization to the first date of documented progression, as determined by the investigator per RECIST 1.1, or death due to any cause, whichever occurs first. Clinical deterioration in the absence of progression per RECIST 1.1 is not considered progression for the purpose of determining PFS. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Subjects who started any subsequent anti-cancer therapy, including tumor directed radiotherapy and tumor directed surgery, without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of the subsequent anti-cancer therapy.

The progression free survival rate at time T is defined as the probability that a subject has not progressed and is alive at time T following randomization.

Further explanation for various censoring scenarios for the definition of PFS are presented in Figure 4.2.7-1
4.3 Exploratory Endpoints

4.3.1 Overall Survival

OS is defined as the time between the date of randomization and the date of death due to any cause. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive. The overall survival rate at time T is defined as the probability that a subject is alive at time T following randomization.

4.3.2 Duration of and Time to Objective Response

Duration of and time to objective response will be measured by the endpoints duration of response (DOR) and time to response (TTR). DOR is defined as the time between the date of first response to the date of first documented tumor progression (per RECIST 1.1) or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last tumor assessment. Subjects who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessments prior to initiation of the subsequent anticancer therapy.
TTR is defined as the time from randomization to the date of the first documented CR or PR.

DOR and TTR will be evaluated for responders (CR or PR) only.

4.3.3 Safety

Overall safety and tolerability will be measured by the incidence of adverse events, serious adverse events, AEs leading to discontinuation, deaths, specific laboratory abnormalities (worst grade) and changes from baseline in each treatment group. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See details in the Core Safety SAP6.

4.3.4 Immunogenicity

Refer to Core Safety SAP6.

4.3.5 Biomarkers

Biomarkers potentially associated with clinical endpoints will be measured by analyzing tumor and blood samples. Biomarker endpoints include, but are not limited to, single-nucleotide polymorphisms (SNPs), proteins in tumor specimens and serum, and immune cell populations.

4.3.6 EORTC QLQ-C30

Evaluation of HRQoL as assessed by the EORTC QLQ-C30 will be measured by mean changes from baseline in the EORTC QLQ-C30 global health status/QoL composite scale and by mean changes from baseline in the remaining EORTC QLQ-C30 scales.

EORTC QLQ-C30 is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 comprises 6 functional scales (physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning, and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status and global quality of life items, responses for all items are 4-point categorical scales ranging from 0 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales.

Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual, as follows:

Functional scales:
- Physical functioning: 

\[(1 - ((Q1+Q2+Q3+Q4+Q5)/5 -1)/3) * 100\]
• Role functioning: \(1 - \frac{(Q6+Q7)}{2-1}/3\) \(*\) 100
• Emotional functioning: \(1 - \frac{(Q21+Q22+Q23+Q24)}{4-1}/3\) \(*\) 100
• Cognitive functioning: \(1 - \frac{(Q20+Q25)}{2-1}/3\) \(*\) 100
• Social functioning: \(1 - \frac{(Q26+Q27)}{2-1}/3\) \(*\) 100

Global health status:
• Global health status/QoL: \(\frac{(Q29+Q30)}{2-1}/6\) \(*\) 100

Symptom scales/items:
• Fatigue: \(\frac{(Q10+Q12+Q18)}{3-1}/3\) \(*\) 100
• Nausea and vomiting: \(\frac{(Q14+Q15)}{2-1}/3\) \(*\) 100
• Pain: \(\frac{(Q9+Q19)}{2-1}/3\) \(*\) 100
• Dyspnea: \(\frac{(Q8)}{1}/3\) \(*\) 100
• Insomnia: \(\frac{(Q11)}{1}/3\) \(*\) 100
• Appetite loss: \(\frac{(Q13)}{1}/3\) \(*\) 100
• Constipation: \(\frac{(Q16)}{1}/3\) \(*\) 100
• Diarrhea: \(\frac{(Q17)}{1}/3\) \(*\) 100
• Financial difficulties: \(\frac{(Q28)}{1}/3\) \(*\) 100

Missing values will be imputed for missing items by “assuming that the missing items have values equal to the average of those items which are present” for any scale in which at least half the items are completed. A scale in which less than half of the items are completed will be treated as missing. This is the method proposed in the scoring manual. A questionnaire will be considered as received if at least one of the 15 scales is non-missing (after imputation).

All questionnaires completed at baseline and on-study will be assigned to a time-point and included in the analysis according to the windowing criteria in Table 4.3.6-1. In case a subject has two on-study assessments within the same window, the assessment closest to the time-point will be used. And, in the case of two assessments at a similar distance to the time-point, the latest one will be chosen. In the event where the subject has no assessment at all in a specific window, the observation will be treated as missing for that time-point.

**Table 4.3.6-1: Time Windows for HRQoL Assessments**

<table>
<thead>
<tr>
<th>Nominal Time-Point</th>
<th>Time Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1 (Baseline)</td>
<td>Prior to first dose on Day 1</td>
</tr>
<tr>
<td>Week 7</td>
<td>Day 2 thru Day 96, inclusive</td>
</tr>
<tr>
<td>Week 16</td>
<td>Day 97 thru Day 120, inclusive</td>
</tr>
</tbody>
</table>
Table 4.3.6-1: Time Windows for HRQoL Assessments

<table>
<thead>
<tr>
<th>Nominal Time-Point</th>
<th>Time Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 20</td>
<td>Day 121 thru Day 148, inclusive</td>
</tr>
<tr>
<td>Week 24</td>
<td>Day 149 thru Day 176, inclusive</td>
</tr>
<tr>
<td>Week 28</td>
<td>Day 177 thru Day 204, inclusive</td>
</tr>
<tr>
<td>Week 32</td>
<td>Day 205 thru Day 232, inclusive</td>
</tr>
<tr>
<td>Week 36</td>
<td>Day 233 thru Day 260, inclusive</td>
</tr>
<tr>
<td>Week 40</td>
<td>Day 261 thru Day 288, inclusive</td>
</tr>
<tr>
<td>Every 4 Weeks thereafter while on treatment</td>
<td>[(Week number) * 7] - 19 thru [(Week number) * 7] + 8, inclusive</td>
</tr>
</tbody>
</table>

4.3.7 EuroQoL EQ-5D

Subjects’ overall health status will be measured by mean changes from baseline in the EQ-5D-3L. EQ-5D essentially has 2 components: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. Once the data have been collected and a database created, a scoring function can be used to assign a value (ie, EQ-5D index score) to self-reported health states from a set of population-based preference weights.

The EQ VAS records the subject’s self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state).

5 SAMPLE SIZE AND POWER

Approximately 102 subjects will be randomized to the 2 treatment arms in a 1:1 ratio in order to target 100 treated subjects (50 per arm). This number of treated subjects was chosen to achieve a sufficient level of precision for a descriptive analysis to estimate the difference in rates of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ between the two treatment arms. Fifty treated subjects per arm will allow estimation of the rate difference within 95% confidence limits of +/- 20% or less and will be supplemented by a qualitative clinical assessment of the type and severity of events to evaluate benefit-risk.

In previously submitted Phase 2/3 studies of nivolumab in combination with ipilimumab (CA209069 and CA209067), AEs in the MedDRA Anaphylactic Reaction SMQ (broad scope) with onset within 2 days after sequential dosing of nivolumab 1 mg/kg combined with ipilimumab
3 mg/kg were reported in 24% of treated subjects. In the current study, if the observed rate of these events is equal to 24% among 50 treated subjects in each arm, then the 95% CI for the difference in rates between arms will be (-16.7%, 16.7%).

Table 5-1 shows the precision that the sample size of 50 treated subjects per arm will provide for estimating rates and rate differences between the treatment arms under different assumed observed rates.

<table>
<thead>
<tr>
<th>Arm A (Co-administration, FRC)</th>
<th>Arm B (Sequential administration)</th>
<th>Arm A - Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>24% (13.1%, 38.2%)</td>
<td>22% (11.5%, 36.0%)</td>
<td>2% (-14.5%, 18.5%)</td>
</tr>
<tr>
<td>24% (13.1%, 38.2%)</td>
<td>24% (13.1%, 38.2%)</td>
<td>0% (-16.7%, 16.7%)</td>
</tr>
<tr>
<td>26% (14.6%, 40.3%)</td>
<td>24% (13.1%, 38.2%)</td>
<td>2% (-15.0%, 19.0%)</td>
</tr>
<tr>
<td>30% (17.9%, 44.6%)</td>
<td>28% (16.2%, 42.5%)</td>
<td>2% (-15.8%, 19.8%)</td>
</tr>
<tr>
<td>30% (17.9%, 44.6%)</td>
<td>30% (17.9%, 44.6%)</td>
<td>0% (-18.0%, 18.0%)</td>
</tr>
</tbody>
</table>

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

Study Baseline

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.

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 be considered as baseline.

If more than one tumor biopsy specimen is available, baseline PD-L1 expression will be determined from the most recently collected specimen (prior to first dose of study treatment) with a measurable result. If all specimens for a given subject are either indeterminate or unknown, then the PD-L1 expression will be considered indeterminate as long as at least one specimen is indeterminate. Otherwise, PD-L1 expression will be considered unknown.

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 30 days (or 100 days depending on analysis) of the last dose of study treatment.

The Post Baseline Period may be further divided into the following sub-periods.

6.1.2.1 Part 1 Treatment Period (Combination Portion)

Part 1 dosing is defined as any medication recorded on ‘Record of Study Medication’ CRF page with a visit label containing the text ‘Cycle 1’, ‘Cycle 2’, ‘Cycle 3’, or ‘Cycle 4’ and with total dose delivered > 0 mg.

On-treatment AEs during the Part 1 Treatment Period will be defined as AEs with an onset date-time on or after the date-time of the first dose of Part 1 study treatment (or with an onset date on or after the day of first dose of Part 1 study treatment if time is not collected or is missing). An AE will be counted as on-treatment during Part 1 if the event occurred within 30 days of the last dose of Part 1 study treatment.

On-treatment evaluations (laboratory tests) during Part 1 will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of Part 1 study treatment. An evaluation will be counted as on-treatment during Part 1 if it occurred within 30 days of the last dose of Part 1 study treatment.

6.1.2.2 Part 2 Treatment Period (Maintenance Portion)

Part 2 dosing is defined as any medication recorded on ‘Record of Study Medication’ CRF page with a visit label containing the text ‘Part 2’ and with total dose delivered > 0 mg.

On-treatment AEs during the Part 2 Treatment Period will be defined as AEs with an onset date-time on or after the date-time of the first dose of Part 2 study treatment (or with an onset date on or after the day of first dose of Part 2 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 Part 2 study treatment.

On-treatment evaluations (laboratory tests) during Part 2 will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of Part 2 study treatment. An evaluation will be counted as on-treatment if it occurred within 30 days (or 100 days depending on analysis) of the last dose of Part 2 study treatment.

### 6.2 Treatment Regimens

The treatment group “as randomized” will be retrieved from the IVRS system:

- **Arm A (Co-Administration, FRC):** Experimental arm: BMS-986214 administered every 3 weeks for 4 doses followed by nivolumab flat dose 480 mg every 4 weeks
- **Arm B (Sequential):** Control arm: nivolumab 1 mg/kg + ipilimumab 3 mg/kg administered every 3 weeks for 4 doses followed by nivolumab flat dose 480 mg every 4 weeks

The treatment group “as treated” will be the same as the “as randomized” unless the subject received the incorrect drug for the entire period of treatment, in which case the subject’s treatment group will be defined as the incorrect drug the subject actually received.

### 6.3 Populations for Analyses

Since the primary objective will be addressed by a safety endpoint, the primary endpoint analysis will be based on all treated subjects. For consistency, the secondary endpoints will use the same analysis population as the primary endpoint (ie, all treated subjects).

- **All Enrolled Subjects:** All subjects who signed an informed consent form and were registered into the IRT.
- **All Randomized Subjects:** All subjects who were randomized to any treatment group. This is the primary dataset for efficacy listings.
- **All Treated Subjects:** All subjects who received at least one dose of any study medication. This is the primary dataset for analysis of study conduct, study population, efficacy (including secondary endpoints), exposure, and safety (including primary endpoint).
- **All Subjects Treated in Part 2:** All subjects who received at least one dose of study medication in the open-label nivolumab flat dose maintenance phase (Part 2).
- **Response-Evaluable Subjects:** All treated subjects with measurable disease at a baseline tumor assessment and at least one on-treatment tumor assessment.
- **PK Subjects:** All treated subjects with available serum time-concentration data.
- **Immunogenicity Subjects:** All treated subjects with available ADA data.
  - Nivolumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 postbaseline nivolumab immunogenicity assessment.
  - Ipilimumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 postbaseline ipilimumab immunogenicity assessment.
• Biomarker Subjects: All treated subjects with available biomarker data.
  - All PD-L1 tested subjects: Treated subjects who had a tumor biopsy specimen assessed for PD-L1 expression. This will be used for analyses of PD-L1 expression
  - All PD-L1 evaluable subjects: All PD-L1 tested subjects with quantifiable PD-L1 expression
  - Biomarker Evaluable Subjects: All Treated Subjects with a baseline measurement and at least one post-baseline sample for the given marker.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, 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) using the mean, standard deviation, median, minimum and maximum values. If a missing category is not being presented in the data display, only those subjects with non-missing values for the parameter being assessed are included in the percentage calculation.

Time to event distribution will be estimated using Kaplan Meier techniques. This will be done for endpoints progression free survival, overall survival and duration of response (note that TTR will be analyzed using summary statistics such as mean, SD, median, min, max). Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survivor function $S(t)^{9,10}$. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula$^{11}$ for variance derivation and on log-log transformation applied on the survivor function $S(t)^{12}$.

Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method$^{13}$.

Formal hypothesis testing with control of Type I error will not be conducted for any of the endpoints in this study. No p-values will be presented. Confidence intervals, when presented, will be for descriptive purposes only and will not be adjusted for multiplicity.

Unless otherwise noted, safety analyses will be performed using the on-treatment definition for the entire study treatment period (i.e. combined Part 1 and Part 2 treatment periods) as defined in Section 6.1.2. Alternate analysis periods will be used for specific endpoints or selected analyses as described in the corresponding endpoint or analysis section of this SAP.

Please see the following sections for additional details:

• Section 4.1: Primary Endpoint: MedDRA Anaphylactic Reaction Broad Scope SMQ AE Incidence Rate
• Section 4.2.1: MedDRA Anaphylactic Reaction Narrow Scope SMQ AE Incidence Rate
• Section 4.2.2: Hypersensitivity/Infusion Reaction Select AE Incidence Rate
• Section 4.2.6: Objective Response Rate
• Section 4.2.7: Progression Free Survival
• Section 4.3.1: Overall Survival
• Section 4.3.2: Duration of and Time to Objective Response
• Table 4.3.6-1: Time Windows for HRQoL Assessments
• Section 7.3.1: Subject Disposition
• Section 7.4.1: Administration of Study Therapy
• Section 7.6.9: Adverse Events

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site, and per month for all randomized subjects. Randomization date (if applicable), first dosing date, country, investigational site will be presented in a by subject listing of accrual.

Furthermore, the accrual pattern will be summarized by the stratification factors PD-L1 status and M Stage.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and summarized by treatment group and overall. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

At Entrance:
• Subjects with baseline ECOG performance status > 1
• Subjects who received prior systemic anti-cancer treatment in the metastatic setting
• Subjects without histologically documented Stage III or Stage IV melanoma, as per AJCC staging system

On-study:
• Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) while on study therapy
• Subjects treated differently than as randomized (subjects who received the wrong treatment, excluding the never treated)

Listings will also be provided.
7.3 Study Population

Summaries of study population will be based on all treated subjects, except that of subject disposition which will be based on all enrolled subjects.

7.3.1 Subject Disposition

The total number of subjects enrolled (randomized or not randomized) will be presented along with the reason for not being randomized. This analysis will be performed on the all enrolled population only.

Number of subjects who discontinued study treatment during Part 1 and during the overall study for All Treated Subjects and during Part 2 for All Subjects Treated in Part 2, along with corresponding reason for discontinuation will be tabulated by treatment group as treated. Reason for discontinuation will be derived from subject status CRF page.

Number of subjects randomized but not treated along with the reason will be tabulated by treatment group as randomized. This analysis will be performed on the all randomized population only.

A subject listing for all randomized subjects will be provided showing the subject’s randomization date (if applicable), first and last dosing date, off study date and reason for going off-study. A subject listing for subjects not randomized will also be provided, showing the subject’s race, gender, age, consent date and reason for not being randomized.

7.3.2 Demographics and Baseline Characteristics

The following baseline characteristics will be summarized by treatment group, for the population of All Treated Subjects. All baseline presentations will identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics)
- Age category I (< 65, ≥ 65- < 75, ≥ 75)
- Age category II (< 65, ≥ 65)
- Gender (male, female)
- Race (white, black, asian, other)
- Region (EU, Australia)
- Baseline ECOG Performance Status (0, 1)
- M Stage at Study Entry (M0, M1a, M1b, M1c) (source: CRF)
- AJCC Stage at Study Entry (III, IV)
- Weight (descriptive statistics)
- PD-L1 Status (≥5%, <5%/indeterminate) (source: clinical database)
- BRAF mutation status (BRAF mutant, wildtype) (source: CRF)
• BRAF mutation test (Cobas+THxID, Other, Unknown)
• Baseline LDH (≤ ULN, > ULN)
• Baseline LDH (≤ 2*ULN, > 2*ULN)
• History of Brain Metastases (Yes, No)
• Smoking Status (Yes, No)
• Time from Initial Disease Diagnosis to Randomization (< 1 year, 1-< 2 year, 2-< 3 year, 3-< 4 year, 4-< 5 year, ≥ 5 year)
• All lesions (Investigator Tumor Assessments at Baseline): sites of disease, number of disease sites per subject.
• Target lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of longest diameter of target lesion.

• Similarly the following IVRS data will be summarized by treatment group as randomized.
  • M Stage at Study Entry (M0/M1a/M1b/M1c)
  • PD-L1 Expression Level (≥5% and <5%/indeterminate)

7.3.3 Medical History
General medical history will be listed by subject.

7.3.4 Prior Therapy
The following will be summarized by treatment group for All Treated Subjects.
• Prior neo-adjuvant therapy (yes/no)
• Prior adjuvant therapy (yes/no)
• Time from completion of prior adjuvant therapy to randomization ( < 6 months and ≥ 6 months) for subjects who received prior adjuvant therapy
• Prior surgery related to cancer (yes/no)
• Prior radiotherapy (yes/no)

Agents and medication will be reported using the generic name. A listing by subject will also be provided.

7.3.5 Baseline Examinations
Subjects with abnormal baseline physical exam results will be tabulated by examination criteria (eg, neck, cardiovascular, lungs, etc) and by treatment group for All Treated Subjects.
### 7.3.6 Discrepancies between IVRS and CRF information

Summary tables (cross-tabulations) of stratification factors for All Treated Subjects by treatment group will be provided to show any discrepancies between what was reported through IVRS vs. CRF data or clinical database (baseline).

- M Stage at Study Entry (IVRS vs. CRF data)
- PD-L1 status (IVRS vs. clinical database)

### 7.4 Extent of Exposure

Analyses will be performed by treatment group “as treated” in all treated subjects, unless otherwise specified.

#### 7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by treatment group:

- Time from randomization to first dose of study therapy (0 to 3 days, > 3 to 7, > 7 to 14, > 14 to 21, > 21 to 28, > 28)
- Number of concomitant doses received (nivolumab + ipilimumab).
  - For Arm B a subject will be considered to have received concomitant doses of nivolumab and ipilimumab if both infusions are administered on the same date.
  - For Arm A a subject will be considered to have received concomitant doses of nivolumab and ipilimumab if any FRC infusion was administered.

The following parameters will be summarized (descriptive statistics) by treatment group and study therapy (nivolumab and ipilimumab for Arm B, BMS-986214 for Arm A). during Part 1 for All Treated Subjects:

- Number of doses received
- Cumulative dose in mg/kg
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%
- Infusion duration in minutes

In addition, the following parameters will be summarized (descriptive statistics) for nivolumab flat dosing during Part 2 for All Subjects Treated in Part 2:

- Number of doses received
- Cumulative dose in mg
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%
- Infusion duration in minutes
Duration of treatment will be presented by treatment group using a Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off study therapy. Median duration of treatment and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date. Duration of study therapy will also be summarized in a table with descriptive statistics (mean, minimum, and maximum). The percentage of subjects with study therapy duration > 3 months, > 6 months, > 9 months, and > 12 months will be tabulated. A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose changes) and a listing of batch numbers will be also provided.
### Table 7.4.1-1: Study Therapy Parameter Definitions During Part 1 (Combination Portion)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMS-986214 (Co-administration FRC)</th>
<th>Nivolumab (Arm B)</th>
<th>Ipilimumab (Arm B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Schedule per Protocol</td>
<td>4 mg/kg every 3 weeks for 4 doses</td>
<td>1 mg/kg every 3 weeks for 4 doses</td>
<td>3 mg/kg every 3 weeks for 4 doses</td>
</tr>
<tr>
<td>Dose</td>
<td>Dose (mg/kg) is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.</td>
<td>Dose (mg/kg) is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.</td>
<td>Dose (mg/kg) is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.</td>
</tr>
<tr>
<td>Cumulative Dose</td>
<td>Cum Dose (mg/kg) is the sum of the doses administered to a subject during Part 1.</td>
<td>Cum Dose (mg/kg) is the sum of the doses administered to a subject during Part 1.</td>
<td>Cum Dose (mg/kg) is the sum of the doses administered to a subject during Part 1.</td>
</tr>
<tr>
<td>Relative Dose Intensity (%)</td>
<td>Cum dose/[4 x (Last Part 1 dose date - Start dose date + 21)/21] x 100</td>
<td>Cum dose/[1 x (Last Part 1 dose date - Start dose date + 21)/21] x 100</td>
<td>Cum dose/[3 x (Last Part 1 dose date - Start dose date + 21)/21] x 100</td>
</tr>
<tr>
<td>Infusion Duration (mins)</td>
<td>Each infusion duration is calculated as infusion stop date/time - infusion start date/time.</td>
<td>Each infusion duration is calculated as infusion stop date/time - infusion start date/time.</td>
<td>Each infusion duration is calculated as infusion stop date/time - infusion start date/time.</td>
</tr>
<tr>
<td>Duration of Treatment</td>
<td>Last Part 1 dose date - Start dose date + 1</td>
<td>Last Part 1 dose date - Start dose date + 1</td>
<td>Last Part 1 dose date - Start dose date + 1</td>
</tr>
</tbody>
</table>

### Table 7.4.1-2: Study Therapy Parameter Definitions During Part 2 (Maintenance)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nivolumab (Arms A and B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Schedule per Protocol</td>
<td>480 mg flat dose every 4 weeks</td>
</tr>
<tr>
<td>Dose</td>
<td>Dose (mg) = total dose delivered as recorded on Record of Study Medication CRF</td>
</tr>
<tr>
<td>Cumulative Dose</td>
<td>Cum Dose (mg) is the sum of the doses administered to a subject during Part 2.</td>
</tr>
<tr>
<td>Relative Dose Intensity (%)</td>
<td>[Cumulative dose (mg) / ( (Last dose date in Part 2 – first dose date in Part 2 + 28) x 480/28)] x 100</td>
</tr>
</tbody>
</table>
Table 7.4.1-2: Study Therapy Parameter Definitions During Part 2 (Maintenance)

<table>
<thead>
<tr>
<th>Nivolumab (Arms A and B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Duration (mins)</td>
</tr>
<tr>
<td>Duration of Treatment</td>
</tr>
</tbody>
</table>

- **Infusion Duration (mins)**: Each infusion duration is calculated as infusion stop date/time - infusion start date/time.
- **Duration of Treatment**: last dose date in Part 2 - first dose date in Part 2 + 1
7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays
Each nivolumab, ipilimumab, or BMS-986214 infusion may be delayed. A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e., greater than or equal to 4 days from scheduled dosing date). All studies drugs must be delayed until treatment can resume. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized by treatment group:
• Number of dose delays per subject, length of delay, and reason for delay

7.4.2.2 Infusion interruptions and Rate Changes
Each nivolumab, ipilimumab, or BMS-986214 infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

The following parameters will be summarized by treatment group:
• Number of subjects with at least one dose infusion interruption, the reason for interruption, and the number of infusion interruptions per subject.
• Number of subjects with at least one IV infusion rate reduction and the reason for reduction.

7.4.2.3 Dose Escalations
Dose escalations are not permitted for any study drug.

7.4.2.4 Dose Reductions
Dose reductions are not permitted for any study drug.

7.4.2.5 Dose Omissions
Dose omissions are not permitted for any study drug.

7.4.3 Concomitant Medications
Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e., on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

The following summary table will be provided:
• Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term)

A by-subject listing will accompany the table.
7.5 Efficacy

The primary endpoint is related to safety and there are no primary efficacy endpoints. Analysis methods for the primary safety endpoint are described in Section 7.6.1. Descriptive analyses of secondary and exploratory efficacy endpoints will be performed and are described below.

7.5.1 Objective Response Rate

ORRs (based on investigator assessments using RECIST 1.1 criteria) and corresponding 95% exact CIs will be calculated using the Clopper Pearson method\textsuperscript{13} for each of the treatment arms. BOR will be tabulated for each treatment group. Associated odds ratios and 95% CIs for Arm A relative to Arm B will be calculated using Cochran-Mantel-Haenszel (CMH) methodology, adjusting for the stratification factors PD-L1 expression and M stage at screening (IVRS source). An estimate of the difference in ORRs and corresponding 2-sided 95% CI will be calculated using CMH methodology, adjusting for the same stratification factors as above.

Subgroup Analysis

To assess consistency of treatment effects in ORR in different subsets, a “forest” plot of the unweighted differences in ORRs and corresponding exact 95% CIs using the Newcombe method\textsuperscript{14} will be produced for the following variables:

- PD-L1 Status ($\geq$5% expression and $<$5% expression/indeterminate) (source: clinical database)
- BRAF mutation status (BRAF mutant and wildtype)
- M Stage at Study Entry (M0/M1a/M1b and M1c) (source: CRF)
- Age category I ($< 65$, $\geq 65 - < 75$, and $\geq 75$)
- Age category II ($< 65$ and $\geq 65$)
- Gender (male and female)
- Race (white, black, asian, and other)
- Region (EU, Australia)
- Baseline ECOG Performance Status (0 and 1)
- History of Brain Metastases (Yes and No)
- Baseline LDH ($\geq$ ULN and $>$ ULN)
- Baseline LDH ($\leq$2*ULN and $>$ 2*ULN)
- AJCC Stage (III and IV)

If a subgroup category has less than 10 subjects per treatment group, ORR will not be computed/displayed.

For purposes of analysis, countries will be included in each region category according to Table 7.5.1-1.
Table 7.5.1-1: Region Definition

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>EU</td>
</tr>
<tr>
<td>Italy</td>
<td>EU</td>
</tr>
<tr>
<td>Spain</td>
<td>EU</td>
</tr>
<tr>
<td>Australia</td>
<td>Australia</td>
</tr>
</tbody>
</table>

Duration of Objective Response

DOR curves in each treatment group will be estimated using the KM product-limit method for subjects with a BOR of CR or PR. Median DOR, corresponding two-sided 95% CI, and range will be reported.

Time to Objective Response

Summary statistics of TTR will be provided by treatment group for subjects with a BOR of CR or PR. TTR curves will be estimated using the KM product-limit method in all treated subjects and will represent the cumulative rate of response over time. For non-responders, subjects will be censored at the maximum time of response + 1 day of all subjects in their respective treatment group. Cumulative response rates will be tabulated at Week 12 and Month 6.

Other Analyses

The following subject-level graphics will be provided by treatment group.

- For responders only, the time course of the following events of interest will be graphically displayed: tumor response, tumor progression, last dose received, and death.
- For response-evaluable subjects (treated subjects with baseline and at least one on-study tumor assessment), a waterfall plot showing the best reduction in target lesion tumor burden based on investigator assessment.

7.5.2 Progression Free Survival

PFS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product limit method in All Treated Subjects. Median PFS and corresponding two-sided, 95% confidence intervals will be computed. Descriptive HRs and corresponding two sided 95% CIs for Arm A relative to Arm B will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by PD-L1 status and M Stage at screening (IVRS source). PFS rates at 6 and 9 months with 95% CIs will be estimated using KM methodology.

The source of progression event (death versus progression) will be summarized by treatment group.

The status of subjects who are censored in the PFS KM analysis will be tabulated for each treatment group using the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdrawn consent, never treated)
- Received subsequent anticancer therapy

### 7.5.3 Overall Survival

OS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. Median OS and corresponding two-sided, 95% confidence intervals will be computed.

Descriptive HRs and corresponding two-sided 95% CIs for Arm A relative to Arm B will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by PD-L1 status and M Stage at screening (IVRS source).

The status of subjects who are censored in the OS KM analysis will be tabulated for each treatment group using the following categories:

- on-study (on-treatment and not progressed, on-treatment progressed, in follow-up)
- off-study: (lost to follow-up, withdrew consent, etc)

Survival rates at 6 and 9 months will be estimated using KM estimates on the OS curve for each treatment group. Associated two-sided 95% CIs will be calculated.

### 7.5.4 Subject Follow-Up

The extent of follow-up defined as the time between randomization date and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively (median, min, max) for all treated subjects in Arms A and B.

The currentness of follow-up, defined as the time between last OS contact (ie, last known date alive or death date) and data cut-off date, will be summarized by treatment group. Subjects who died before data cut-off date will automatically have zero value for currentness of follow-up. For subjects with last known date alive after data cut-off date, they will have zero value for currentness of follow-up as well. The currentness of follow-up will be categorized into the following categories: 0 days, 1-30 days, 31-60 days, 61-90 days, 91-120 days, 121-150 days, 151 or more days.

### 7.5.5 Subsequent Therapy

Subsequent therapy and response to subsequent therapy will be summarized and listed.

- Subsequent Therapy
  - Chemotherapy by drug name
  - Hormonal or biologic therapy by drug name
  - Immunotherapy (anti-PD1 agents, anti-PDL1 agents, anti-CTLA4 agents, and others) by drug name
  - BRAF inhibitor by drug name
- MEK/NRAS inhibitor by drug name
- Other investigational agent by drug name
- Surgery
- Radiotherapy
- Any combination of the above

- By Subject Listing of Subsequent Therapy

### 7.5.6 Interim Analysis

Not applicable.

### 7.6 Safety

#### 7.6.1 MedDRA Anaphylactic Reaction Broad Scope SMQ AE Incidence Rate

For purposes of the primary endpoint analysis, the incidence rate of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after any dose in the Part 1 dosing period will be reported by treatment arm for all treated subjects. Corresponding 95% CIs for the rate in each treatment arm will be calculated using the Clopper-Pearson method. An estimate and confidence interval for the difference in rates between treatment arms will be presented based on CMH method of weighting, adjusting for PD-L1 status and M Stage at screening.

Additional characterization of the events meeting the primary endpoint criteria will be provided, including summaries by system organ class (SOC) and preferred term (PT). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the most recent version of the dictionary at the time of the database lock will be used. Adverse events results will be graded for severity using NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 criteria. In the AE summary tables subjects will be counted by worst CTC grade only once at the Preferred Term (PT), only once at the System Organ Class (SOC), and only once at subject level for the counting of total number of subjects with an AE. The AE tables will list the SOCs (ordered by descending frequency) and the PTs (ordered by descending frequency within each SOC) for each treatment group.

#### 7.6.2 MedDRA Anaphylactic Reaction Narrow Scope SMQ AE Incidence Rate

The incidence rate of Anaphylactic reactions based on MedDRA narrow scope SMQ by treatment arm, the difference in rates between arms, and the corresponding 95% confidence intervals will be reported using the same methods as described above for the primary endpoint analysis. Summaries by worst CTC grade, SOC, and PT will also be provided similar to the primary endpoint.

#### 7.6.3 Hypersensitivity/Infusion Reaction Select AE Incidence Rate

The incidence rate of hypersensitivity/infusion reaction select AEs by treatment arm, the difference in rates between arms, and the corresponding 95% confidence intervals will be reported using the
same methods as described above for the primary endpoint analysis. Summaries by worst CTC grade, SOC, and PT will also be provided similar to the primary endpoint.

7.6.4  **Drug-related and All Causality Grade 3-5 AEs Incidence Rates**
Analyses of drug-related and all causality Grade 3-5 AEs will be aligned with the Core Safety SAP as described in Section 7.6.9.

7.6.5  **Deaths**
See Core Safety SAP6.

7.6.6  **Serious Adverse Events**
See Core Safety SAP6.

7.6.7  **Adverse Events Leading to Discontinuation of Study Therapy**
See Core Safety SAP6.

7.6.8  **Adverse Events Leading to Dose Modification**
See Core Safety SAP6.

7.6.9  **Adverse Events**
See Core Safety SAP6. Summaries of AEs and drug-related AEs will also be provided separately for events with onset during the Part 1 treatment period for All Treated Subjects and for events with onset during the Part 2 treatment period for All Subjects Treated in Part 2. These additional summaries by treatment period will be performed using the 30-day safety window only.

7.6.10  **Select Adverse Events**
See Core Safety SAP6.

7.6.11  **Immune Modulating Medication**
See Core Safety SAP6.

7.6.12  **Multiple Events**
See Core Safety SAP6.

7.6.13  **Other Events of Special Interest**
See Core Safety SAP6.
**7.6.14 Immune-Mediated Adverse Events**

See Core Safety SAP\(^6\).

**7.6.15 Laboratory Parameters**

See Core Safety SAP\(^6\). Lipase and Amylase will be added to the list of lab parameters to be summarized.

**7.6.16 Vital Signs and Pulse Oximetry**

See Core Safety SAP\(^6\).

**7.6.17 Immunogenicity Analysis**

See Core Safety SAP\(^6\).

**7.6.18 Pregnancy**

See Core Safety SAP\(^6\).

**7.6.19 Adverse Events By Subgroup**

See Core Safety SAP\(^6\). Categories for region will be the same as those specified in Section 7.5.1.
7.8.2 Other Biomarkers

If data are available, the following parameters and their corresponding change (or percent change) from baseline will be summarized for biomarker evaluable subjects by treatment arm and timepoint using descriptive statistics (N, mean, median, standard deviation, minimum, maximum):

- Peripheral T cells subsets (activated and proliferating CD4 and CD8 T cells: ICOS+CD3+CD4+, ICOS+CD3+CD8+, CTLA4+CD3+CD4+, CTLA4+CD3+CD8+, PD-1+CD3+CD4+, PD-1+CD3+CD8+, ki67+CD3+CD4+, ki67S+CD3+CD8+)
- MDSCs (myeloid-derived suppressor cells)
- Serum cytokines (with emphasis on interferon-gamma, interferon-gamma-stimulated cytokines: IFN-gamma, CXCL9, CXCL10)

A by-subject listing of these biomarkers measures will be provided.

7.9 Outcomes Research

7.9.1 EORTC QLQ-C30

Analysis of EORTC QLQ-C30 will be performed in all treated patients who have an assessment at baseline and at least one follow-up assessment. All scales and single items are scored on a categorical scale and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health/quality of life and higher scores for a symptom scale representing higher level of symptoms.

Baseline measures will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for each scale by treatment group, based on all treated subjects with a baseline measurement.
Change from baseline will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for each scale at each assessment time point by treatment group. A plot summarizing the mean change from baseline for the global health score and each scale of the EORTC QLQ-C30 will be presented. These analyses will be performed in all treated subjects who have an assessment at baseline and at least one on-study assessment.

EORTC QLQ-C30 questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (ie, number of subjects on treatment or in follow up), will be calculated and summarized for each assessment time point by treatment group.

### 7.9.2 EuroQol EQ-5D

Unless otherwise specified, the analysis of EQ-5D will be performed in all treated subjects who have an assessment at baseline and at least one or more post-baseline assessments.

Subject’s overall health state on a visual analog scale (EQ-VAS) and change from baseline in EQ-VAS at each assessment time point will be summarized by treatment group using descriptive statistics (N, mean, SD, median, 25th and 75th percentiles, minimum, maximum). A plot summarizing the mean change from baseline in EQ-VAS will be presented.

Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem and by treatment group. Percentages will be based on number subjects assessed at assessment time point.

EQ-5D questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (ie, number of subjects on treatment or in follow up), will be calculated and summarized for each assessment time point by treatment group.

EQ-5D Index values will be computed using a scoring algorithm based on the UK MVH-A1 TTO value set. Change from baseline in EQ-5D Index score at each assessment time point will be summarized by treatment group using descriptive statistics (N, mean, SD, median, 25th and 75th percentiles, minimum, maximum). A plot summarizing the mean change from baseline in EQ-5D Index score will be presented.

A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

### 8 CONVENTIONS

See Core Safety SAP.

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 not covered by Core Safety SAP, 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)

9 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.