Official Title of Study: Phase II, Randomized, Study of Multiple Administration Regimens for Nivolumab plus Ipilimumab in Subjects with Renal Cell Carcinoma

NCT Number: NCT03029780

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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) CA209800

VERSION # 1.0

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Research Hypothesis:

Treatment with BMS-986237 will demonstrate no clinically relevant differences in safety relative to nivolumab and ipilimumab administered sequentially in patients with renall cell carcinoma.

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 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 be approximately 9 months (6 months of accrual plus an additional 3 months to ensure all subjects who are still on-treatment have completed Part 1 period)
- from start of randomization to final analysis of the study is expected be approximately 15 months (6 months of accrual plus an additional 9 months of minimum follow-up 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 II, open-label, randomized 2-arm study of the fixed ratio combination (BMS-986237) of nivolumab and ipilimumab in a 3:1 ratio (nivolumab 3 mg/kg and ipilimumab 1 mg/kg) in subjects with previously untreated advanced or metastatic RCC.

Subjects meeting all eligibility criteria will be randomized 1:1 ratio and stratified by IMDC prognostic score (0 vs 1-2 vs 3-6) to Arm A (BMS-986237) or Arm B (nivolumab and ipilimumab administered sequentially).

In Part 1, Arm A, BMS-986237 will be administered as one 60-minute infusion, every 3 weeks for up to 4 doses.

In Part 1, Arm B, nivolumab and ipilimumab will be administered sequentially within the same day, as two separate infusions, one 60-minute nivolumab infusion and one 30-minute ipilimumab infusion with a 30-minute break between each infusion, every 3 weeks for up to 4 doses.

Six weeks after the last dose in Part 1, subjects will then receive nivolumab 480 mg flat dose infused over 30 minutes every four weeks in Part 2 until progression or unacceptable toxicity.

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.

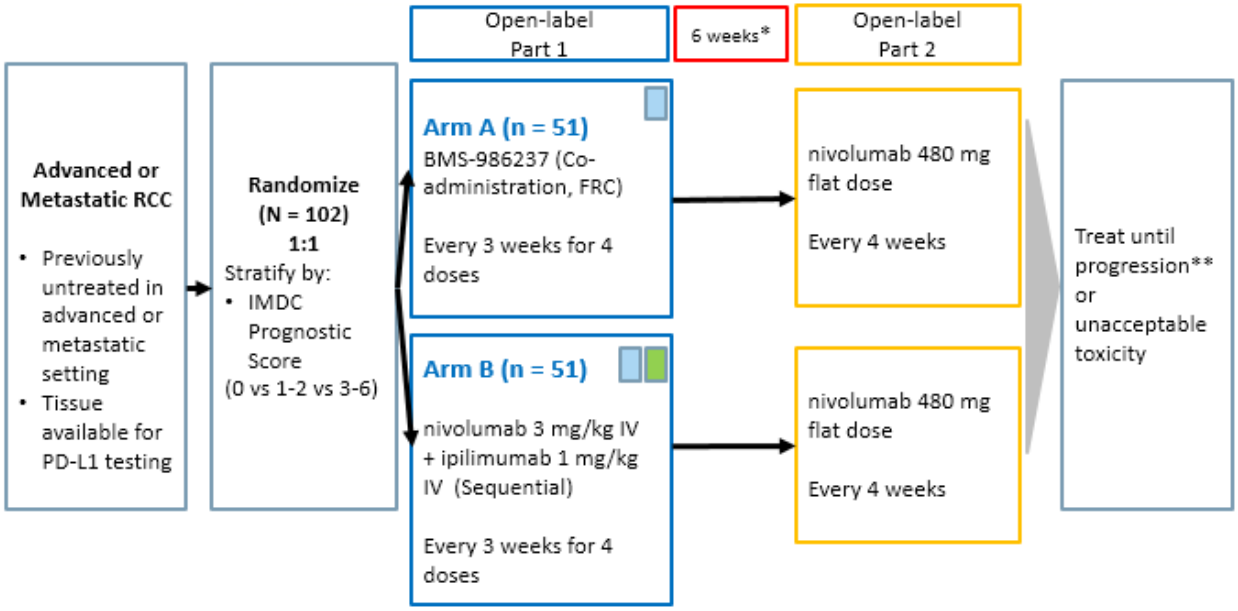
In addition, study safety is evaluated on an ongoing basis by representatives of BMS Global Pharmacovigilance and the BMS medical safety team (MST), who operate independently from the clinical team and monitor safety across all nivolumab protocols, identify potential safety signals, notify appropriate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

The study population for this trial will include adult subjects (≥ 18 years) with histological confirmation of RCC with a clear-cell component.

Subjects who advance to Part 2 will be treated until progression or unacceptable toxicity.

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

Figure 2.1-1: Study Design Schematic



*6 weeks from last combination dose in Part 1 to first nivolumab monotherapy dose in Part 2
**Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.

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. All subjects will be centrally randomized or 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.

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
- IMDC prognostic score (0 vs 1-2 vs 3-6)

Subjects meeting all eligibility criteria will be randomized 1:1 ratio and stratified by IMDC prognostic score (0 vs 1-2 vs 3-6) to Arm A (BMS-986237) or Arm B (nivolumab and ipilimumab administered sequentially).

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 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
Revised Protocol 01 (Incorporates Amendment 01 and Administrative Letter 01)	18-JAN-2017	Incorporate additional safety parameters and clarifications as per the FDA guidance following the submission of IND 132265 . Clarify inconsistencies in the original protocol as per the review of local Ethical Committees. Correct typo errors on the original protocol Delete one of the eligibility criteria in the protocol synopsis (and align it with the text in the eligibility criteria section of the protocol body) that was erroneously included in the original protocol.
Revised Protocol 02	2-AUG-2017	Adding clarifications to the protocol Correcting inconsistencies and text that was erroneously deleted in the Revised Protocol 01.

3 OBJECTIVES

3.1 Primary

The primary objective is to evaluate the difference in safety between co-administered FRC nivolumab 3 mg/kg and ipilimumab 1 mg/kg relative to sequentially administered nivolumab 3 mg/kg and ipilimumab 1 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.

3.2 Secondary

- To evaluate incidence of AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ
- To evaluate drug-related Grade 3 - 5 AE incidence rate defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria
- To evaluate causality Grade 3 - 5 AE incidence rate defined using 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 subjects who are still on-treatment complete Part 1 period.

Table 4.1-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term[a]	Term Scope[b]
Acute respiratory failure	Broad
Allergic oedema	Broad
Anaphylactic reaction	Narrow
Anaphylactic shock	Narrow
Anaphylactic transfusion reaction	Narrow
Anaphylactoid reaction	Narrow
Anaphylactoid shock	Narrow
Angioedema	Broad
Asthma	Broad
Blood pressure decreased	Broad
Blood pressure diastolic decreased	Broad
Blood pressure systolic decreased	Broad
Bronchial oedema	Broad
Bronchospasm	Broad
Cardiac arrest	Broad
Cardio-respiratory arrest	Broad
Cardio-respiratory distress	Broad
Cardiovascular insufficiency	Broad
Chest discomfort	Broad
Choking	Broad
Choking sensation	Broad
Circulatory collapse	Narrow
Circumoral oedema	Broad
Cough	Broad
Cyanosis	Broad
Dialysis membrane reaction	Narrow
Diastolic hypotension	Broad
Dyspnoea	Broad
Erythema	Broad
Eye oedema	Broad
Eye pruritus	Broad
Eye swelling	Broad
Eyelid oedema	Broad
Face oedema	Broad
Flushing	Broad
Generalised erythema	Broad

Table 4.1-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term[a]	Term Scope[b]
Hyperventilation	Broad
Hypotension	Broad
Injection site urticaria	Broad
Irregular breathing	Broad
Kounis syndrome	Narrow
Laryngeal dyspnoea	Broad
Laryngeal oedema	Broad
Laryngospasm	Broad
Laryngotracheal oedema	Broad
Lip oedema	Broad
Lip swelling	Broad
Mouth swelling	Broad
Nasal obstruction	Broad
Nodular rash	Broad
Ocular hyperaemia	Broad
Oedema	Broad
Oedema mouth	Broad
Oropharyngeal spasm	Broad
Oropharyngeal swelling	Broad
Periorbital oedema	Broad
Pruritus	Broad
Pruritus allergic	Broad
Pruritus generalised	Broad
Rash	Broad
Rash erythematous	Broad
Rash generalised	Broad
Rash pruritic	Broad
Respiratory arrest	Broad
Respiratory distress	Broad
Respiratory failure	Broad
Reversible airways obstruction	Broad
Sensation of foreign body	Broad
Shock	Narrow
Shock symptom	Narrow
Skin swelling	Broad
Sneezing	Broad

Table 4.1-1: Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term[a]	Term Scope[b]
Stridor	Broad
Swelling	Broad
Swelling face	Broad
Swollen tongue	Broad
Tachypnoea	Broad
Throat tightness	Broad
Tongue oedema	Broad
Tracheal obstruction	Broad
Tracheal oedema	Broad
Type I hypersensitivity	Narrow
Upper airway obstruction	Broad
Urticaria	Broad
Urticaria papular	Broad
Wheezing	Broad

[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 Part 1 period. The efficacy-related secondary analysis will be analyzed at the time of final analysis when all patients 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 Drug-Related Grade 3 - 5 AE Incidence Rate

The second 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.

4.2.3 All Causality Grade 3 - 5 AE Incidence Rate

The third 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.

4.2.4 Pharmacokinetic Analyses

The fourth 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.

4.2.5 Objective Response Rate

The fifth 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. 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 including radiotherapy, tumor-directed surgery, or systematic anticancer therapy, whichever occurs first. For subjects without documented progression or first 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.

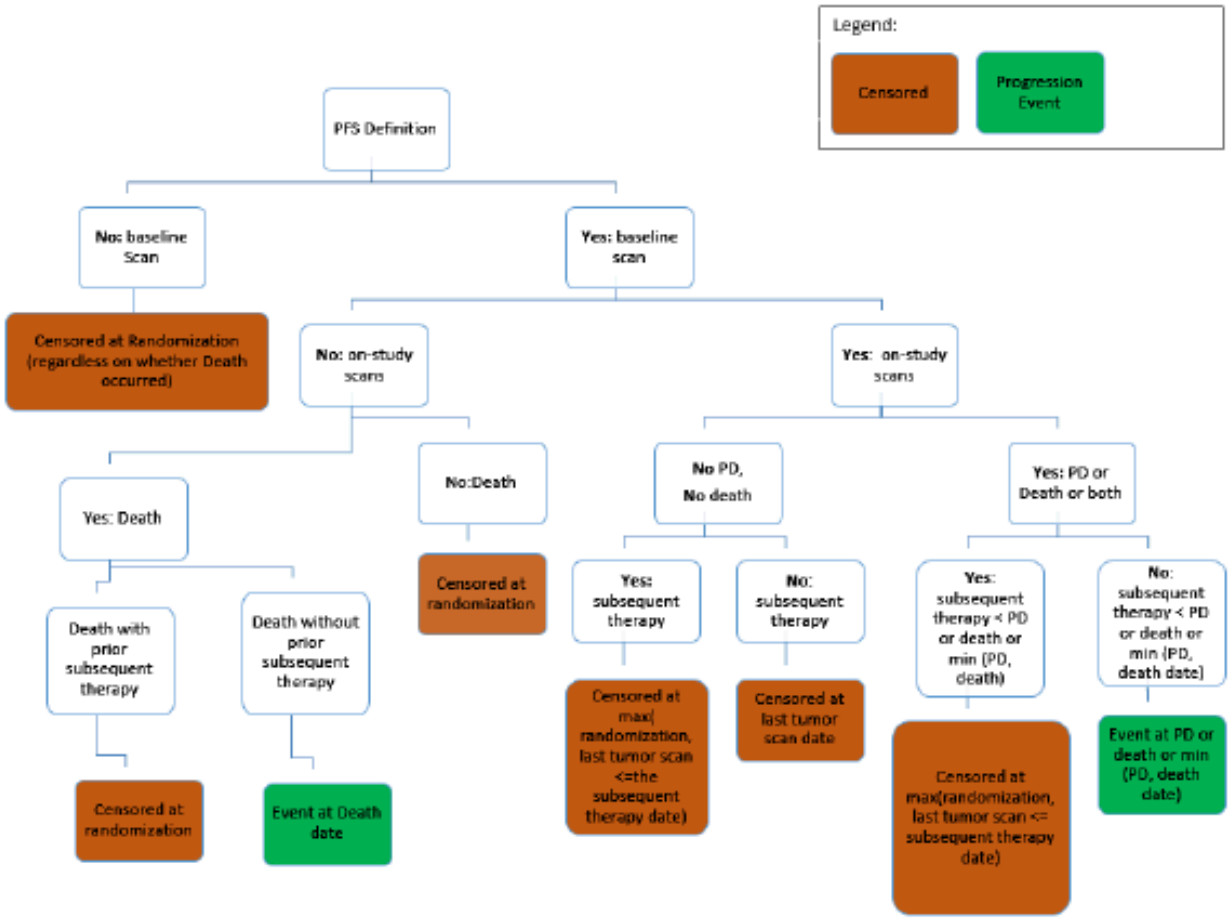
4.2.6 Progression Free Survival

The sixth 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, tumor directed surgery, or systematic anticancer therapy, 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

Figure 4.2.7-1: Graphic Display of PFS Definition



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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. The 20% limit represents what is considered to be a clinically meaningful difference in the rates of infusion-related reactions.

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 infusion reactions 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 5-1: 95% CI for Rates and Rate Differences when Observed in 50 Subjects per Arm

Observed AE Rate (95% CI)		Observed Rate Difference (95% CI)
Arm A (Co-administration, FRC)	**Arm B (Sequential administration)**	**Arm A - Arm B**
24% (13.1%, 38.2%)	22% (11.5%, 36.0%)	2% (-14.5%, 18.5%)
24% (13.1%, 38.2%)	24% (13.1%, 38.2%)	0% (-16.7%, 16.7%)
26% (14.6%, 40.3%)	24% (13.1%, 38.2%)	2% (-15.0%, 19.0%)
30% (17.9%, 44.6%)	28% (16.2%, 42.5%)	2% (-15.8%, 19.8%)
30% (17.9%, 44.6%)	30% (17.9%, 44.6%)	0% (-18.0%, 18.0%)

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-986237 administered every 3 weeks for 4 doses followed by nivolumab flat dose 480 mg every 4 weeks
- Arm B (Sequential): Control arm: nivolumab 3 mg/kg + ipilimumab 1 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).

Population	Description
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 Treated Subjects 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.
Pharmacokinetic 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.
[redacted]	[redacted]

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)[4,5]. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula[6] for variance derivation and on log-log transformation applied on the survivor function S(t)[7].

Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[8].

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:

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 factor IMDC prognastic score.

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 KPS < 70%
- Subjects who received prior systemic anti-cancer treatment in the metastatic setting
- Subjects without histologically confirmed RCC with a clear-cell component, documented advanced or metastatic (AJCC Stage IV) RCC

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 for All Treated Subjects,
- 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 (< 65, ≥ 65- < 75, ≥ 75)
- Gender (male, female)
- Race (White, Black or African American, Asian, Other)
- Ethnicity (Hispanic/Latino and Not Hispanic/Latino)
- Region (US, Australia, Chile; per IVRS)
- Karnofsky performance status (100, 90, 80, 70, <70)
- IMDC prognostic score (0, 1-2, ≥ 3) (source: CRF)
- Weight (descriptive statistics)
- PD-L1 expression summary (0-1%; 1-5%; 5-10%; 10%)
- Hemoglobin (<LLN, ≥ LLN)
- Alkaline phosphatase (< ULN, ≥ ULN)
- LDH level (≤ 1.5 x ULN, >1.5 x ULN)
- Corrected Calcium (≤ 10 mg/dl, >10mg/dl)
- History of Brain Metastases (Yes, No)
- Time from initial disease diagnosis to randomization (<1 year, ≥1 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.

- IMDC prognostic score (0, 1-2, ≥ 3)

7.3.3 Medical History

General medical history will be listed by subject.

7.3.4 Prior Therapy

- Prior adjuvant or neo-adjuvant therapy agents for compelety resectable RCC will be summarized by treatment group for All Treated Subjects..

7.3.5 Baseline Examinations

Subjects with abnormal baseline physical examination will be tabulated by examination criteria and by treatment group for All Treated Subjects.

7.3.6 Discrepancies between IVRS and CRF information

Summary tables (cross-tabulations) of the stratification factor for All Treated Subjects by treatment group will be provided to show any discrepancies between what was reported through IRT vs. CRF data.

- IMDC prognostic score (0, 1-2, ≥ 3) (IRT vs. CRF data)

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) and number of nivolumab flat doses received.
  - 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-986237 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 same set of parameters will be summarized (descriptive statistics) for nivolumab flat dosing during Part 2 for All Subjects Treated in Part 2:

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)

	BMS-986237 (Co-administration FRC)	Nivolumab (Arm B)	Ipilimumab (Arm B)
Dosing Schedule per Protocol	4 mg/kg every 3 weeks for 4 doses	3 mg/kg every 3 weeks for 4 doses	1 mg/kg every 3 weeks for 4 doses
Dose	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.	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.	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.
Cumulative Dose	Cum Dose (mg/kg) is the sum of the doses administered to a subject during Part 1.	Cum Dose (mg/kg) is the sum of the doses administered to a subject during Part 1.	Cum Dose (mg/kg) is the sum of the doses administered to a subject during Part 1.
Relative Dose Intensity (%)	Cum dose/[(Last Part 1 dose date - Start dose date + 21) × 4/21] × 100	Cum dose/[(Last Part 1 dose date - Start dose date + 21) × 3/21] × 100	Cum dose/[(Last Part 1 dose date - Start dose date + 21) x 1/21] × 100
Infusion Duration (mins)	Each infusion duration is calculated as infusion stop date/time - infusion start date/time.	Each infusion duration is calculated as infusion stop date/time - infusion start date/time.	Each infusion duration is calculated as infusion stop date/time - infusion start date/time.
Duration of Treatment	*Last Part 1 dose date - Start dose date +1*	*Last Part 1 dose date - Start dose date +1*	*Last Part 1 dose date - Start dose date +1*

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

	Nivolumab (Arms A and B)
Dosing Schedule per Protocol	480 mg flat dose every 4 weeks
Dose	Dose (mg) = total dose delivered as recorded on Record of Study Medication CRF
Cumulative Dose	Cum Dose (mg) is the sum of the doses administered to a subject during Part 2.
Relative Dose Intensity (%)	[Cum dose (mg) /((Last dose date in Part 2 – First dose date in Part 2 + 28) × 480/28)] × 100
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-986237 infusion may be delayed. A dose will be considered as actually delayed if the delay is exceeding 3 days (ie 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-986237 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.

[redacted]

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 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 factor IMDC prognostic score (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 factor as above.

Subgroup Analysis (Arms A and B only): 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[9] will be produced for the following variables:

- IMDC prognostic score (0, 1-2, ≥ 3) (source: clinical database)
- Age category (< 65, ≥ 65- < 75, and ≥ 75)
- Gender (male and female)
- Race (white, black, asian, and other)
- Region (US, Chile, Australia)
- Karnofsky performance status (< 90 vs. ≥ 90)
- History of Brain Metastases (Yes and No)
- Time from initial disease diagnosis to randomization (<1 year, ≥1 year)
- LDH level (≤ 1.5 x ULN, >1.5 x ULN)
- Hemoglobin (<LLN, ≥ LLN)
- Corrected Calcium (≤ 10 mg/dl, >10mg/dl)
- Alkaline phosphatase (< ULN, ≥ ULN)
- Baseline PD-L1+ status based on a 1% cut off
- Baseline PD-L1+ status based on a 5% cut off
- Baseline PD-L1+ status based on a 10% cut off

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

Duration of Objective Response (DOR): 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 IMDC prognastic score at screening (IVRS source). PFS rates at 6 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

[redacted]

[redacted]

Survival rates at 6 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 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 IMDC prognastic score 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.

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 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 7.6.8.

7.6.4 Deaths

See Core Safety SAP[1].

7.6.5 Serious Adverse Events

See Core Safety SAP[1].

7.6.6 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP[1].

7.6.7 Adverse Events Leading to Dose Modification

See Core Safety SAP[1].

7.6.8 Adverse Events

See Core Safety SAP[1]. 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.

7.6.9 Select Adverse Events

See Core Safety SAP[1].

7.6.10 Immune Modulating Medication

See Core Safety SAP[1].

7.6.11 Multiple Events

See Core Safety SAP[1].

7.6.12 Other Events of Special Interest

See Core Safety SAP[1].

7.6.13 Immune-Mediated Adverse Events

See Core Safety SAP[1].

7.6.14 Laboratory Parameters

See Core Safety SAP[1]. Lipase and Amylase will be added to the list of lab parameters to be summarized.

7.6.15 Vital Signs and Pulse Oximetry

See Core Safety SAP[1].

7.6.16 Immunogenicity Analysis

See Core Safety SAP[1].

7.6.17 Pregnancy

See Core Safety SAP[1].

7.6.18 Adverse Events By Subgroup

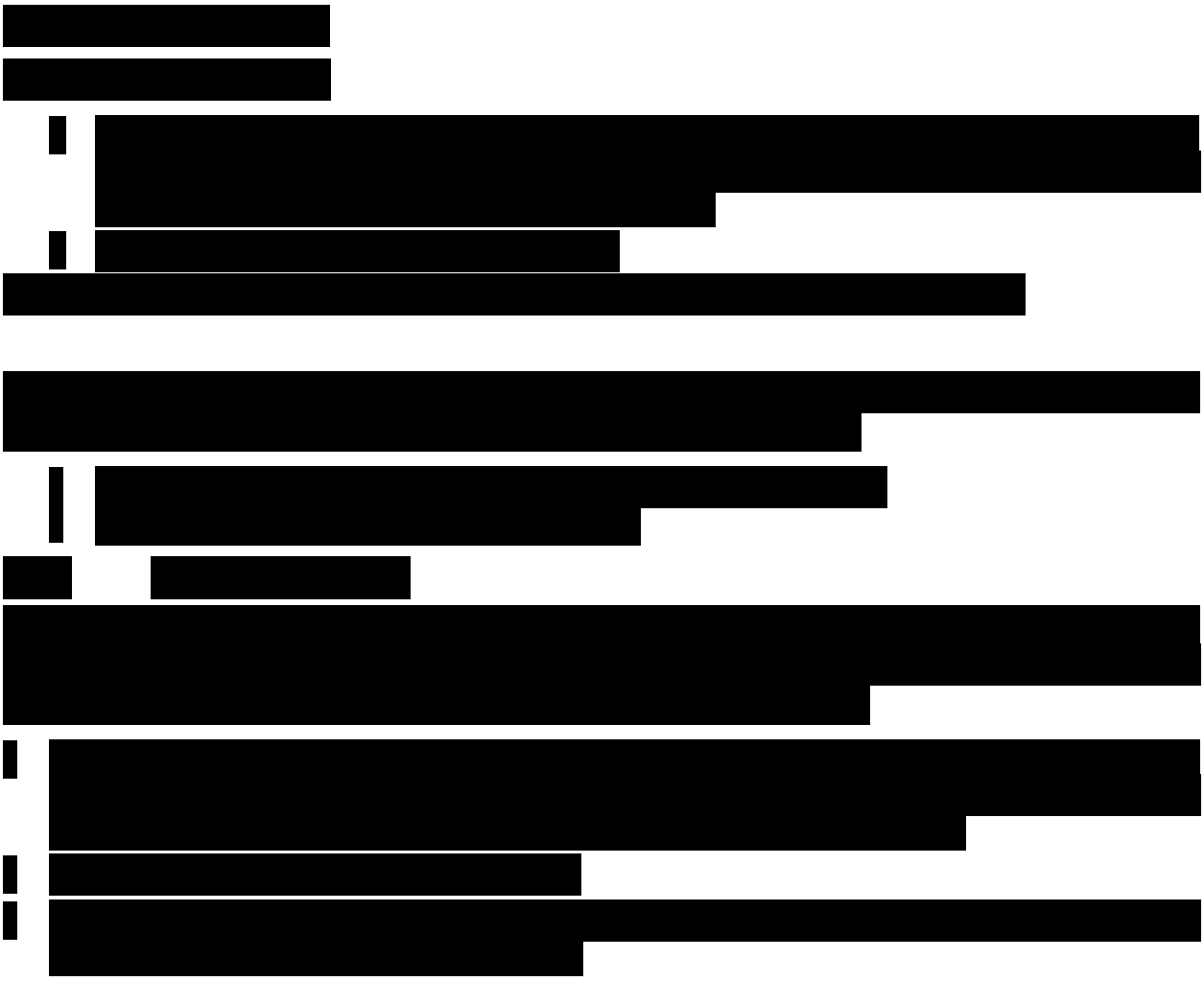
See Core Safety SAP[1]. Categories for region will be the same as those specified in Section 7.5.1

7.7 Pharmacokinetics

For purposes of the secondary endpoint, PK comparisons will be summarized using descriptive summary statistics to compare nivolumab and ipilimumab predose and end of infusion (EOI) concentrations administered as FRC to that of sequentially administered nivolumab and ipilimumab. End of infusion and trough (predose) concentration levels of nivolumab and ipilimumab will be summarized by treatment arm and study day using descriptive statistics (N, mean, SD, geometric mean, %CV, median, minimum, and maximum).). Graphs of geometric mean trough concentrations of nivolumab and ipilimumab, and also the geometric mean End of Infusion (EOI) concentrations of nivolumab and ipilimumab vs. study day by treatment arm will be provided for visual comparison of FRC vs. sequential administration of nivolumab and ipilimumab.

The nivolumab and ipilimumab concentration vs time data obtained in this study may be combined with data from other studies in the clinical development program to develop a population PK model, if needed, to compare model based PK parameters and exposure following administration of the FRC and sequential administration. This model will be used to determine measures of individual exposure (such as single dose and steady state peak, trough and timeaveraged concentrations). If conducted, the results of the population PK analyses will be reported separately.

[redacted]



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

7.9 Outcomes Research

7.9.1 FACT-G

Descriptive statistics (mean, standard deviation, median, first and third quartiles, minimum, maximum) will be calculated for the difference from baseline for each item at each period. These analyses will be based on all treated subjects who have a baseline measurement and an on-study assessment for the time-point of interest. Summary statistics on the difference from baseline over time will be prepared for each scale.

7.9.2 FKSI-19

Descriptive summary statistics of the FKSI-19 total score and each subscale score (Disease Related Symptoms-Physical (DRS-P), Disease Related Symptoms-Emotional (DRS-E), Treatment Side Effects (TSE), Function/Well-Being (FWB)) will be presented at baseline and each on-study time

point. Mean changes from baseline for each of the outcome assessments will be calculated for each participant at each on-study time point.

The questionnaire completion rate for the FKSI-19, defined as the proportion of questionnaires received out of the expected number (i.e., the number of subjects still on study), will be calculated and summarized at each assessment time point. Missing data will not be imputed for the analyses.

A by-subject listing of FKSI-19 question score, total score, and each sub scale score will be provided.

7.9.3 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[10, 11]. 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[1].

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.

[redacted]