

Official Title of Study:

Phase IIIb/IV, Randomized, Double Blinded, Study of Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg vs Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma
(CheckMate 511: CHECKpoint pathway and nivoluMAB clinical Trial Evaluation 511)

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**STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT**

**PHASE IIIB/IV, RANDOMIZED, DOUBLE BLINDED, STUDY OF NIVOLUMAB 3
MG/KG IN COMBINATION WITH IPILIMUMAB 1 MG/KG VS NIVOLUMAB 1 MG/KG
IN COMBINATION WITH IPILIMUMAB 3 MG/KG IN SUBJECTS WITH PREVIOUSLY
UNTREATED, UNRESECTABLE OR METASTATIC MELANOMA**

PROTOCOL(S) CA209511

VERSION # 1.0

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2 STUDY DESCRIPTION

2.1 Study Design

The main study is a Phase IIIb/IV, randomized, double blind, 2-arm study of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg vs nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg, in adult (≥ 18 years) subjects 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 will be randomized 1:1 and stratified by PD-L1 status and AJCC M stage as described below:

- PD-L1 expression level
 - PD-L1 $\geq 5\%$ tumor cell surface expression (in a minimum of a hundred evaluable tumor cells) vs
 - PD-L1 $< 5\%$ tumor cell surface expression (in a minimum of a hundred evaluable tumor cells)/indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)
- AJCC M stage at screening
 - M0/M1a/M1b vs
 - M1c

It is expected that 460 subjects will need to be enrolled in order to randomize 346 in Arms A and B, assuming a screen failure rate of 25%.

The study design schematic is presented in [Figure 2.1-1](#) and [Figure 2.1-2](#).

Figure 2.1-1: Study Design Schematic Arms A and B

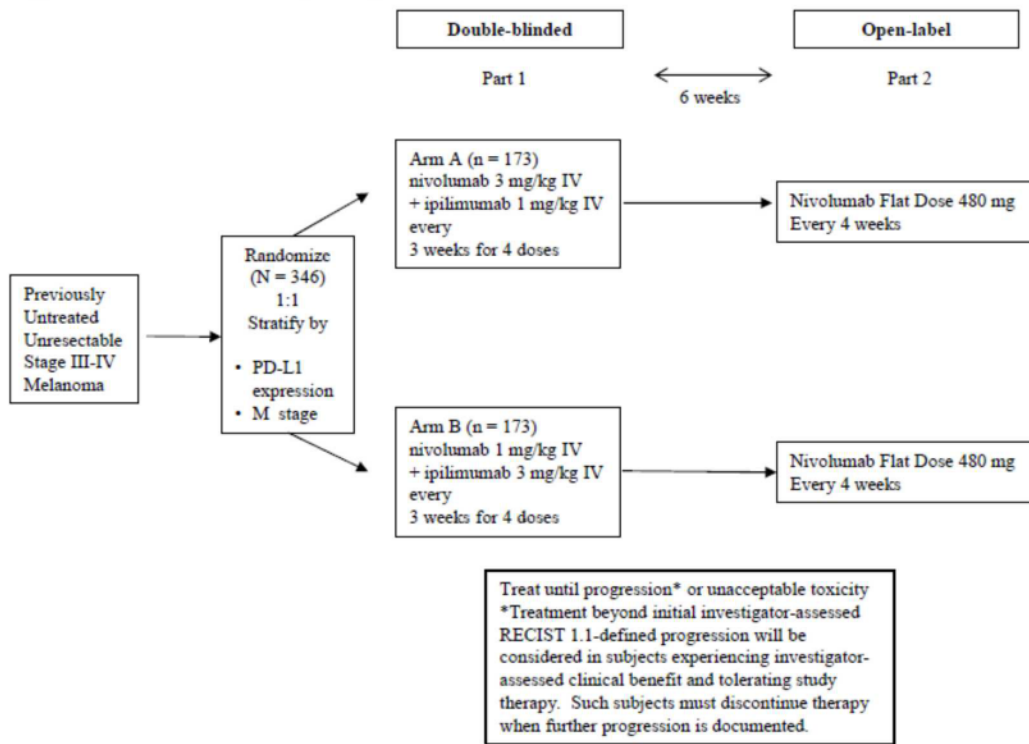
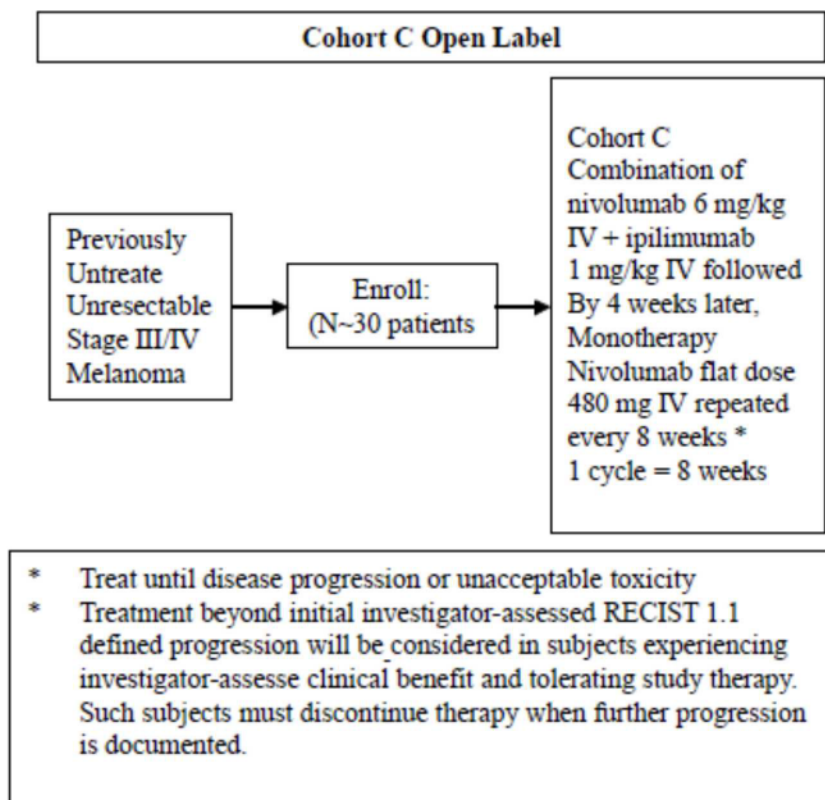


Figure 2.1-2: Study Schematic for Cohort C



At selected sites, the Cohort C will be added, once the accrual in the randomized study has been completed.

This cohort (Cohort C) will be an uncontrolled and open-label single-treatment group with the same inclusion/exclusion criteria as the main CA209511 trial. The patients will be treated, in a non-randomized fashion without stratification, with nivolumab 6 mg/kg plus ipilimumab 1 mg/kg followed by nivolumab 480 mg Flat Dose 4 weeks later and repeated every 8 weeks. M-staging, PDL-1 status and BRAF status must be collected in eCRF but is not mandated prior to treatment.

At activation of this amendment at selected sites, approximately 25 subjects will be treated by a combination dose and schedule of nivolumab plus ipilimumab (Cohort C). This amendment impacts study conduct at CA209511 selected sites in selected countries. This amendment does not impact study conduct at any other CA209511 sites.

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.

Arms A and B:

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 \geq 5% expression vs PD-L1 $<$ 5% expression/indeterminate) entered by vendor
- M Stage at screening

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to Arm A (N3I1) or Arm B (N1I3) and stratified by PD-L1 expression level (PD-L1 \geq 5% expression vs PD-L1 $<$ 5% expression/indeterminate) and M stage (M0/M1a/M1b vs M1c). The randomization procedures will be carried out via permuted blocks within each stratum.

Cohort C (at Selected Sites):

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

- Subject number
- Date of birth.

Subjects meeting all eligibility criteria will be assigned to Cohort C (N6I1) and will not be stratified.

2.3 Blinding and Unblinding

Arms A and B:

The sponsor, subjects, investigator, and site staff will be blinded to the study drug administered during Part 1 (Combination Portion) of the study. Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned by sponsor to provide oversight of drug supply and other unblinded study documentation.

During Part 2 (monotherapy portion), 480 mg nivolumab administered as a flat dose will be open-label. However, subject's treatment assigned arm during Part 1 must not be revealed until end of study.

In the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Designated staff of Bristol-Myers Squibb Research & Development may be unblinded prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

Cohort C (at Selected Sites):

This cohort will be an uncontrolled and open-label single-treatment group, and therefore blinding and unblinding is not applicable to Cohort C.

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 03)	08-Jan-2016	The interval between the end of the combination regimen (Part 1) and the beginning of the nivolumab flat dose monotherapy (Part 2) has been amended from 3 weeks to 6 weeks. The simultaneous administration of the nivolumab and ipilimumab regimen planned in Part 1 of the treatment phase has been removed from the current protocol and will be tested in a distinct trial.
Amendment Number 05 Site Specific: All Sites in The Netherlands	13-Apr-2016	The purpose of this site-specific amendment is to add an evaluation of the PET tracer [18F]-BMS-986192 as a biomarker for PD-L1 expression in melanoma subjects, and to assess PD-L1 changes by PET following immune therapy with the combination of nivolumab and ipilimumab. This amendment impacts study conduct at CA209511 site in the Netherlands and will be implemented after IRB review and approval. This amendment does not impact study conduct at any other CA209511 sites. Up to 30 subjects will have PET scans under this amendment.
Revised Protocol 02	31-Aug-2016	To reflect updates in the nivolumab investigator brochure (IB 15):

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
(Incorporates Amendment 07)		<p>modifications were made to management algorithms (Appendix 4)</p> <p>To reflect updates to the acceptable methods of contraception (Appendix 5).</p> <p>Other changes were madet o resolve minor inconsistencies or to provide clarifications.</p>
<p>Amendment Number 08</p> <p>Site Specific: Selected Sites in Canada, France and Spain participating in Cohort C</p>	28-Sep-2016	<p>Add Cohort C to the current CA209511 trial to investigate the overall safety and tolerability of nivolumab 6 mg/kg + ipilimumab 1 mg/kg followed 4 weeks later by nivolumab 480 mg flat dose, this regimen being repeated q8w.</p>

3 OBJECTIVES

3.1 Primary

The primary objective is to compare the incidence of drug-related Grade 3 - 5 AEs of N3I1 to N1I3 in subjects with previously untreated, unresectable or metastatic melanoma.

3.2 Secondary

- To evaluate the ORR, as determined by investigators, of N3I1 and N1I3 in subjects with untreated, unresectable or metastatic melanoma.
- To evaluate PFS of N3I1 and N1I3 in subjects with untreated, unresectable or metastatic melanoma.
- To assess OS of N3I1 and N1I3 in subjects with untreated, unresectable or metastatic melanoma.
- To evaluate Health Related Quality of Life (HRQoL) of N3I1 and N1I3 as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30.

[REDACTED]



4 ENDPOINTS

4.1 Primary Endpoint: Rate of Drug-related Grade 3-5 AEs

The primary endpoint of the study is the rate of drug-related Grade 3 - 5 adverse events in Arms A and B. 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. AE grade will be defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria.

The analysis of the primary endpoint will occur when all treated subjects who are still on-treatment have had at least 2 post-baseline tumor assessments.

4.2 Secondary Endpoints

Secondary endpoints will be analyzed at the time of the primary endpoint analysis.

4.2.1 Objective Response Rate

The first secondary endpoint is ORR in Arms A and B 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.

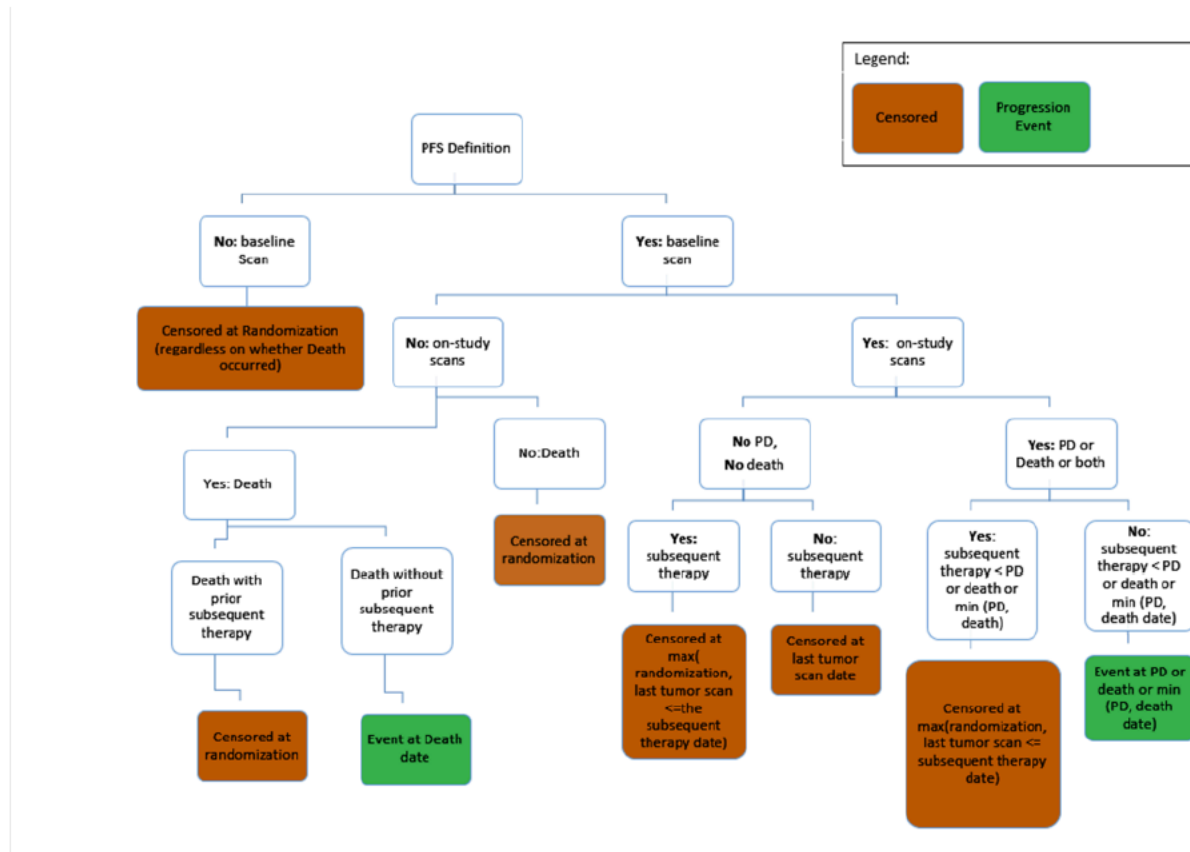
4.2.2 Progression Free Survival

The second secondary endpoint is PFS in Arms A and B. 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 4.2.2-1](#)

Figure 4.2.2-1: Graphic Display of PFS Definition



4.2.3 Overall Survival

The third secondary endpoint is OS in Arms A and B. 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 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 SAP¹.

4.3.3 Immunogenicity




Refer to Core Safety SAP¹.

4.3.4 Pharmacokinetics

Pharmacokinetics will be measured using serum concentration-time data of nivolumab and ipilimumab. Samples will be collected to characterize pharmacokinetics of nivolumab administered alone or in combination with ipilimumab.

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.



4.3.7 ORR, PFS, and OS in Cohort C

ORR, PFS, and OS for Cohort C will be defined similarly to the other arms, except that these endpoints will be measured from the first dosing date rather than the randomization date.

5 SAMPLE SIZE AND POWER

Approximately 346 subjects will be randomized to the 2 treatment arms A and B in a 1:1 ratio in order to target 340 treated subjects (170 per arm). Given a two-sided alpha of 0.05, this number of treated subjects provides 80% power to show a statistically significant difference in the rate of drug-related Grade 3 - 5 AEs between the two treatment arms, assuming a rate of 40% in Arm A and a rate of 55% in Arm B.

We assume that treatment with N3I1 (Arm A) will result in a 15% reduction in the rate of drug-related Grade 3 - 5 events when compared to treatment with N1I3 (Arm B). The difference of 15% is clinically meaningful and assumes a 40% event rate in Arm A and a 55% event rate in Arm B. The assumption of 55% in Arm B is based on observed rates of drug-related Grade 3 - 5 AEs in the combination arm of studies CA209069 and CA209067, which enrolled the same patient population as the current study (previously untreated metastatic melanoma). The assumed reduction to 40% in Arm A corresponds to the same rate ratio (0.727) that was observed in Cohort 2a relative to Cohort 2 in Study CA209004.

Table 8.1-1 shows the precision that the sample size of 170 treated subjects per arm will provide for estimating adverse event rates (primary endpoint) or objective response rates (secondary endpoint), under different assumed observed rates.

For example, if exactly 68 of 170 treated subjects (40%) experience a drug-related Grade 3 - 5 AE in Arm A and 94 of 170 treated subjects (55.3%) experience a drug-related Grade 3 - 5 AE in Arm B, then the exact 95% CI for the rate of drug-related Grade 3 - 5 AEs will be (32.6%, 47.8%) for Arm A and (47.5%, 62.9%) for Arm B.

Furthermore, if exactly 102 of 170 treated subjects (60%) experience an objective response in a treatment arm, then the exact 95% CI for the ORR in that treatment arm will be (52.2%, 67.4%). If the observed ORR is exactly the same in each arm and equal to 60%, then the 95% CI for the difference in ORR between arms will be (-10.4%, 10.4%), and the 95% CI for the odds ratio will be (0.65, 1.54).

Table 5-1: Exact 95% CI for Rates when Observed in 170 Subjects

Number Subjects with Event	Observed Rate	Lower limit Exact 95% CI	Upper limit Exact 95% CI
68	40.0%	32.6%	47.8%
77	45.3%	37.7%	53.1%
85	50.0%	42.2%	57.8%
94	55.3%	47.5%	62.9%
102	60.0%	52.2%	67.4%

Following completion of enrollment into Arm A and Arm B of the main study, approximately 25 additional subjects will be treated in an independent Cohort C for purposes of an exploratory sub-study. Subjects in Cohort C will not be included in the primary analysis and will be evaluated descriptively in a separate report.

Thus the total number of subjects expected to be treated in the CA209511 study is 365, consisting of 340 treated in the randomized double-blind main study and 25 treated in the open label exploratory sub-study (Cohort C).

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.

Baseline for Part 2 Treatment Period

Baseline evaluations or events for the Part 2 Treatment Period will be defined as evaluations or events that occur before the date and time of the first dose of Part 2 study treatment. Evaluations on the same date and time of the first dose of Part 2 study treatment will be considered as baseline evaluations. Conventions for handling missing or not collected time and multiple assessments will be as described above except that the Part 2 dosing date will replace the study dosing date.

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 'Part 1' and with total volume infused > 0 mL.

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 (or 100 days depending on analysis) 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 (or 100 days depending on analysis) 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

Arms A and B:

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

- Arm A (N3I1): Experimental 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
- Arm B (N1I3): 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”** as long as the subject received at least one dose of study medication.

Cohort C:

All subjects will be assigned nivolumab 6 mg/kg + ipilimumab 1 mg/kg administered every 8 weeks alternating with a flat dose of 480 mg nivolumab every 8 weeks. The treatment group **“as treated”** will be the same as the assigned treatment as long as the subject received at least one dose of study medication.

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).

Arms A and B:

- 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 were randomized to Arm A or Arm B and 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 were randomized to Arm A or Arm B and 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.

Cohort C:

- All Treated Subjects: All subjects who enrolled into Cohort C and received at least one dose of any study medication.
- All Enrolled Subjects, Response Evaluable Subjects, PK Subjects, Immunogenicity Subjects, and Biomarker Subjects are defined the same as for Arms A and B above.

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 formula⁶ 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 method⁸.

Formal hypothesis testing with control of Type I error will only be conducted for the primary endpoint. In addition, descriptive analyses of secondary efficacy endpoints will be performed to evaluate the hypothesis of similar efficacy between the treatment arms A and B. The P-values and confidence intervals for these secondary analyses are for descriptive purposes only and will not be adjusted for multiplicity.

Subjects in Cohort C will not be included in the primary analysis and will be evaluated descriptively in a separate report.

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 (Arms A and B) and for all treated subjects (Cohort C). 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

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

For Arms A and B 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. For Cohort C the total number of subjects enrolled (treated or not) will be presented along with the reason for not being treated.

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment group as treated. Reason for discontinuation will be derived from subject status CRF page. This analysis will be performed on the population of All Treated Subjects as well as the population of All Subjects Treated in Part 2.

For Arms A and B 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 (Arms A and B) and for all treated subjects (Cohort C).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. For Arms A and B 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 as well as the population of All Subjects Treated in Part 2. All baseline presentations will identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics)
- Age category I (< 65, ≥ 65)
- Age category II (< 65, ≥ 65- < 75, ≥ 75)
- Gender (male, female)
- Race (white, black, asian, other)
- Region (US, EU, Australia, Rest of World)
- 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 for Arms A and B 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 (< 6 months and ≥ 6 months) for subjects who received prior adjuvant therapy
 - For subjects in Arms A and B time will be measured to randomization.
 - For subjects in Cohort C time will be measured to first dose of study 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 in Arms A and B 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

Arms A and B:

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. A subject will be considered to have received concomitant doses of nivolumab and ipilimumab if both infusions are administered on the same date. This summary will be repeated for the subset of subjects in Arm A or Arm B who experienced a drug-related Grade 3-5 AE, as specified in the primary endpoint definition (Section 4.1).

The following parameters will be summarized (descriptive statistics) by treatment group and study therapy (nivolumab and ipilimumab). 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

This summary will be repeated for the subset of subjects in Arm A or Arm B who experienced a drug-related Grade 3-5 AE, as specified in the primary endpoint definition (Section 4.1).

In addition, the following parameters will be summarized (descriptive statistics) by treatment group 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.

This summary will be repeated for the subset of subjects in Arm A or Arm B who experienced a drug-related Grade 3-5 AE, as specified in the primary endpoint definition (Section 4.1).

Cohort C:

The following parameters will be summarized (descriptive statistics):

- Number of concomitant doses received (nivolumab + ipilimumab) and number of nivolumab flat doses received. A subject will be considered to have received concomitant doses of nivolumab and ipilimumab if both infusions are administered on the same date.

The following parameters will be summarized (descriptive statistics) by study therapy (nivolumab and ipilimumab)

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

For Arm A, Arm B, and Cohort C 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. This table will be repeated for the subset of subjects in Arm A or Arm B who experienced a drug-related Grade 3-5 AE, as specified in the primary endpoint definition (Section 4.1).

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 for Arms A and B During Part 1 (Combination Portion)

	Nivolumab Arm A	Nivolumab Arm B	Ipilimumab Arm A	Ipilimumab Arm B
Dosing Schedule per Protocol	3 mg/kg every 3 weeks for 4 doses	1 mg/kg every 3 weeks for 4 doses	1 mg/kg every 3 weeks for 4 doses	3 mg/kg every 3 weeks for 4 doses
Dose	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)
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.	Cum Dose (mg/kg) is the sum of the doses administered to a subject during Part 1.
Relative Dose Intensity (%)	$\text{Cum dose} / [3 \times (\text{Last Part 1 dose date} - \text{Start dose date} + 21) / 21] \times 100$	$\text{Cum dose} / [1 \times (\text{Last Part 1 dose date} - \text{Start dose date} + 21) / 21] \times 100$	$\text{Cum dose} / [1 \times (\text{Last Part 1 dose date} - \text{Start dose date} + 21) / 21] \times 100$	$\text{Cum dose} / [3 \times (\text{Last Part 1 dose date} - \text{Start dose date} + 21) / 21] \times 100$
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.	Each infusion duration is calculated as infusion stop date/time - infusion start date/time.
Duration of Treatment	<i>Last Part 1 dose date - Start dose date +1</i>	<i>Last Part 1 dose date - Start dose date +1</i>	<i>Last Part 1 dose date - Start dose date +1</i>	<i>Last Part 1 dose date - Start dose date +1</i>

Table 7.4.1-2: Study Therapy Parameter Definitions for Arms A and B 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 (%)	$[\text{Cumulative dose (mg)} / ((\text{Last dose date in Part 2} - \text{first dose date in Part 2} + 28) \times 480/28)] \times 100$
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

Table 7.4.1-3: Study Therapy Parameter Definitions for Cohort C

	Nivolumab	Ipilimumab
Dosing Schedule per Protocol	6 mg/kg followed 4 weeks later by 480 mg flat dose repeated every 8 weeks	1 mg/kg every 8 weeks
Dose (mg/kg) for weight based dosing	Dose administered (mg)/Most recent weight (kg).	Dose administered (mg)/Most recent weight (kg).
Dose (mg) for flat dosing	total dose delivered as recorded on Record of Study Medication CRF	N/A
Cumulative Dose (mg/kg) for weight based dosing	the sum of the weight based doses administered to a subject	the sum of the weight based doses administered to a subject
Cumulative Dose (mg) for flat dosing	the sum of the flat doses administered to a subject	N/A
Relative Dose Intensity (%) for weight based dosing	$\text{Cum dose (mg/kg)} / [(\text{Last dose date} - \text{Start dose date} + 56) \times 6/56] \times 100$	$\text{Cum dose (mg/kg)} / [(\text{Last dose date} - \text{Start dose date} + 56) \times 1/56] \times 100$

Table 7.4.1-3: Study Therapy Parameter Definitions for Cohort C

	Nivolumab	Ipilimumab
Relative Dose Intensity (%) for flat dosing	$\left[\frac{\text{Cumulative dose (mg)}}{(\text{Last dose date} - \text{start dose date} + 56) \times 480/56} \right] \times 100$	N/A
Relative Dose Intensity (%)	$1/2 * [\text{Relative Dose Intensity (\%)} \text{ for weight based dosing} + \text{Relative Dose Intensity (\%)} \text{ for flat dosing}]$	Same as Relative Dose Intensity (%) for weight based dosing

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

Each nivolumab and ipilimumab 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) for both nivolumab and ipilimumab. 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 or ipilimumab 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 either nivolumab or ipilimumab.

7.4.2.4 Dose Reductions

Dose reductions are not permitted for either nivolumab or ipilimumab.

7.4.2.5 Dose Omissions

Dose omissions are not permitted for either nivolumab or ipilimumab.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (ie, 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 endpoints will be performed to evaluate the hypothesis of similar efficacy between the treatment arms A and B.

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 method⁸ for each of the treatment arms. BOR will be tabulated for each treatment group. The 2 treatment arms A and B will be compared using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by PD-L1 expression and M stage at screening (IVRS source). Associated odds ratios and 95% CIs for Arm A relative to Arm B will be calculated, and a p-value will be presented for descriptive purposes. An estimate of the difference in ORRs between Arms A and B and corresponding 95% CI will be calculated using CMH methodology, adjusting for the stratification factors PD-L1 expression and M stage at screening.

Sensitivity Analysis (Arms A and B only)

Similar analyses of ORR will be performed using the following modification:

- ORR using the strata as determined at baseline (CRF source for M-stage, clinical database for PD-L1). This analysis will be performed only if the IVRS value for one stratification factor differs from the baseline value in at least 10% of treated subjects.

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 method⁹ 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 and ≥ 65)
- Age category II (< 65 , ≥ 65 - < 75 , and ≥ 75)
- Gender (male and female)
- Race (white, black, asian, and other)
- Region (EU, Non-EU)
- Baseline ECOG Performance Status (0 and 1)
- History of Brain Metastases (Yes and No)
- Baseline LDH (\geq ULN and $>$ ULN)

- Baseline LDH ($\leq 2 \times \text{ULN}$ and $> 2 \times \text{ULN}$)
- 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

Country	Region
Denmark	EU
France	EU
Germany	EU
Italy	EU
Netherlands	EU
Poland	EU
Spain	EU
United Kingdom	EU
Australia	Non-EU
Canada	Non-EU
Israel	Non-EU
Russia	Non-EU
United States	Non-EU

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 randomized 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). A p-value from a 2-sided log-rank test stratified by PD-L1 expression and M stage at screening will be presented for descriptive purposes. 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

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). No p-values will be presented for the OS endpoint.

The status of subjects who are censored in the OS KM analysis will be tabulated for each treatment group using 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 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. A similar summary will be provided for all treated subjects in Cohort C, except that time will be measured from the first dosing date rather than the randomization date.

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 Rate of Drug-related Grade 3-5 AEs

For purposes of the primary endpoint analysis, the drug-related Grade 3 - 5 AE rate for All Treated Subjects in Arms A and B will be reported by treatment arm. Corresponding 95% CIs for the rate

in each treatment arm will be calculated using the Clopper-Pearson method. A p-value from a two-sided CMH test stratified by PD-L1 status and M Stage at screening (IVRS source) will be provided to compare the drug-related Grade 3 - 5 AE rate between the two treatment arms. Associated odds ratios and 95% CIs for Arm A relative to Arm B will be calculated. An estimate of the difference in rates (Arm A - Arm B) and corresponding 95% CI for the difference will be calculated using CMH methodology, adjusting for the same stratification factors.

Additional characterization of drug-related Grade 3-5 AEs will be provided, including summaries by system organ class (SOC) and preferred term (PT) during the entire treatment period and during the Part 1 treatment period and the Part 2 treatment period separately. These analyses are described further in Section 7.6.6.

7.6.2 Deaths

See Core Safety SAP¹. In addition, a separate death summary will be provided for the population of All Subjects Treated in Part 2.

7.6.3 Serious Adverse Events

See Core Safety SAP¹. Summaries of SAEs and drug-related SAEs with onset during the Part 2 treatment period (using the 30-day safety window only) will also be provided for All Subjects Treated in Part 2.

7.6.4 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP¹. Summaries of AEs leading to discontinuation and drug-related AEs leading to discontinuation with onset during the Part 2 treatment period (using the 30-day safety window) will also be provided for All Subjects Treated in Part 2.

7.6.5 Adverse Events Leading to Dose Modification

See Core Safety SAP¹.

7.6.6 Adverse Events

See Core Safety SAP¹. 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.

7.6.7 Select Adverse Events

See Core Safety SAP¹. In addition, the following analyses will be provided for events with onset during the Part 2 treatment period (using the 30-day safety window only) for All Subjects Treated in Part 2.

- Incidence of select AEs
- Incidence of drug-related select AEs

- Time-to resolution of select AE
- Time-to resolution of select AE where immune modulating medication was initiated
- Time-to resolution of drug-related select AE
- Time-to resolution of drug-related select AE where immune modulating medication was initiated

7.6.8 Immune Modulating Medication

See Core Safety SAP¹.

7.6.9 Multiple Events

See Core Safety SAP¹. In addition, a table showing the total number and rate (exposure adjusted) of occurrences for all AEs with onset during the Part 2 treatment period (using the 30-day safety window) will also be provided for All Subjects Treated in Part 2.

7.6.10 Other Events of Special Interest

See Core Safety SAP¹.

7.6.11 Immune-Mediated Adverse Events

See Core Safety SAP¹. Summaries of IMAEs with onset during the Part 2 treatment period and time to resolution of IMAEs with onset during the Part 2 treatment period will also be provided for All Subjects Treated in Part 2.

7.6.12 Laboratory Parameters

See Core Safety SAP¹. Lipase and Amylase will be added to the list of lab parameters to be summarized. The summaries for hematology, serum chemistry, and electrolytes will be repeated for results collected during the Part 2 treatment period for All Subjects Treated in Part 2.

7.6.13 Vital Signs and Pulse Oximetry

See Core Safety SAP¹.

7.6.14 Immunogenicity Analysis

See Core Safety SAP¹.

7.6.15 Pregnancy

See Core Safety SAP¹.

7.6.16 Adverse Events By Subgroup

See Core Safety SAP¹. Categories for region will be the same as those specified in [Section 7.5.1](#)

7.7 Pharmacokinetics

The nivolumab and ipilimumab concentration vs time data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and ipilimumab to determine measures of individual exposure (such as steady state peak, trough and time-averaged concentration). Pharmacokinetic drug- drug interaction between nivolumab and ipilimumab will be studied by population PK approach as appropriate. Model determined exposures may be used for exposure-response analyses of selected efficacy and safety endpoints. The results of population PK, pharmacokinetic drug interaction and exposure response analyses will be reported separately, as needed.

7.8 Biomarkers

Analyses for PD-L1 from tumor tissue specimens, myeloid derived suppressor cells (MDSCs), serum cytokines, and peripheral T cell subsets are described below. Methodology for other biomarkers (including evaluation of the PET tracer [18F]-BMS-986192 as a biomarker for PD-L1 expression) will be detailed in a separate biomarker SAP.

7.8.1 PD-L1

Analyses of PD-L1 expression are descriptive in nature and intended to examine the distribution of PD-L1 expression and assess potential associations between PD-L1 expression and efficacy measures.

PD-L1 status is a categorical variable by X% cut off for quantifiable PD-L1 expression:

- High expression: $\geq X\%$ PD-L1 expression
- Low expression: $< X\%$ PD-L1 expression

where X denotes the PD-L1 expression cut-off of 1%, 5% and 10%. Additional cut off values may also be explored.

PD-L1 expression quartile is a quartilized variable of quantifiable PD-L1 expression from the pooled population.

Analyses of PD-L1 will include:

- Examine the distribution of PD-L1 expression
 - Assess potential association between PD-L1 expression quartile and PD-L1 status and efficacy measures
 - Assess potential association between PD-L1 expression quartile and PD-L1 status and overall AEs
- 1) Descriptive statistics of PD-L1 expression and PD-L1 status, analyses will be based on all PD-L1 evaluable subjects if not otherwise specified

- a) Listing of all PD-L1 IHC data, all PD-L1 tested subjects
 - b) Summary of tumor specimen acquisition and characteristics, all treated subjects
 - c) Summary statistics of PD-L1 expression by treatment groups of select subgroups, and overall.
 - d) Box plot of PD-L1 expression by treatment group and overall
 - e) Cumulative distribution plot of PD-L1 expression versus population percentile by treatment group and overall
 - f) Waterfall plots of individual PD-L1 expression by treatment group
 - g) Frequency of PD-L1 expression quartile and Status (X%), including indeterminate and unknown if over 5% of subjects fall in this category, by treatment group for select subgroups and overall, all PD-L1 tested subjects. Selected subgroups are identical to the subgroups used for ORR subgroup analysis ([Section 7.5.1](#)).
- 2) Evaluation of associations between PD-L1 expression quartile and PD-L1 status and efficacy measures. Analyses will be based all PD-L1 tested subjects if not otherwise specified. Each analysis will be performed for the subgroups listed below if not otherwise specified
- a) Each PD-L1 expression quartile subgroup
 - b) Each PD-L1 status subgroup
 - c) PD-L1 unknown or indeterminate subgroup

Analyses for ORR (BOR):

- Box plots of PD-L1 expression versus Response Status by treatment group

For each of the subgroups:

- Frequency and percentage of investigator-assessed BOR will be summarized for each treatment group.
- Investigator-assessed ORR will be computed by treatment group along with exact 95% CIs using the Clopper-Pearson method.

Analyses for PFS endpoint:

For each of the subgroups:

- PFS curves for each treatment group will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median PFS will be constructed based on a log-log transformed CI for the survivor function.
- For Arms A and B, Forest plot of Hazard Ratios with 95% CIs

Analyses for OS endpoint:

For each of the subgroups:

- OS curves for each treatment group will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median OS will be constructed based on a log-log transformed CI for the survivor function.

- For Arms A and B, Forest plot of Hazard Ratios with 95% CIs

3) Association of all AE and PD-L1 expression, all treated, PD-L1 tested subjects

Overall summary of any AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT by treatment group for following subgroups will be provided

- Each PD-L1 status subgroup (using 1% and 5% thresholds only)
- PD-L1 unknown or indeterminate subgroup.

7.8.2 Other Biomarkers

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



7.9.2 *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) at each assessment time point will be summarized by treatment group using descriptive statistics (N, mean, SD, median, 25th and 75th percentiles,).

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.

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.

Results of EQ5D-Index will be presented separately and will be described in the GHEOR SAP.

8 CONVENTIONS

See Core Safety SAP¹.

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.

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.

