Official Title of Study:

A Phase III, Randomized, Open Label Trial of Nivolumab in combination with Ipilimumab Versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in unresectable Pleural Mesothelioma (CheckMate 743: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 743)

NCT Number: NCT02899299

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A Phase III, Randomized, Open Label Trial of Nivolumab in combination with Ipilimumab Versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in unresectable Pleural Mesothelioma (CheckMate 743: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 743)

PROTOCOL CA209743

VERSION # 1.1

DATE : 07-NOV-2019

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Schedule of Analyses:

A formal interim analysis for the OS is planned after 403 deaths have been observed. This formal comparison of OS will allow for early stopping for superiority. An independent statistician external to BMS will perform the analysis.

The final OS analysis is targeted to occur when at least 473 deaths events have been observed among randomized subjects.

2 STUDY DESCRIPTION

2.1 Study Design

Protocol CA209743 is a randomized (1:1), open-label, Phase 3 trial in subjects ≥ 18 years old with untreated unresectable MPM, evaluating nivolumab combined with ipilimumab versus pemetrexed plus cisplatin or carboplatin as a first line treatment.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first treatment. It is expected that 800 subjects will be enrolled, and approximately 600 subjects will be randomized.

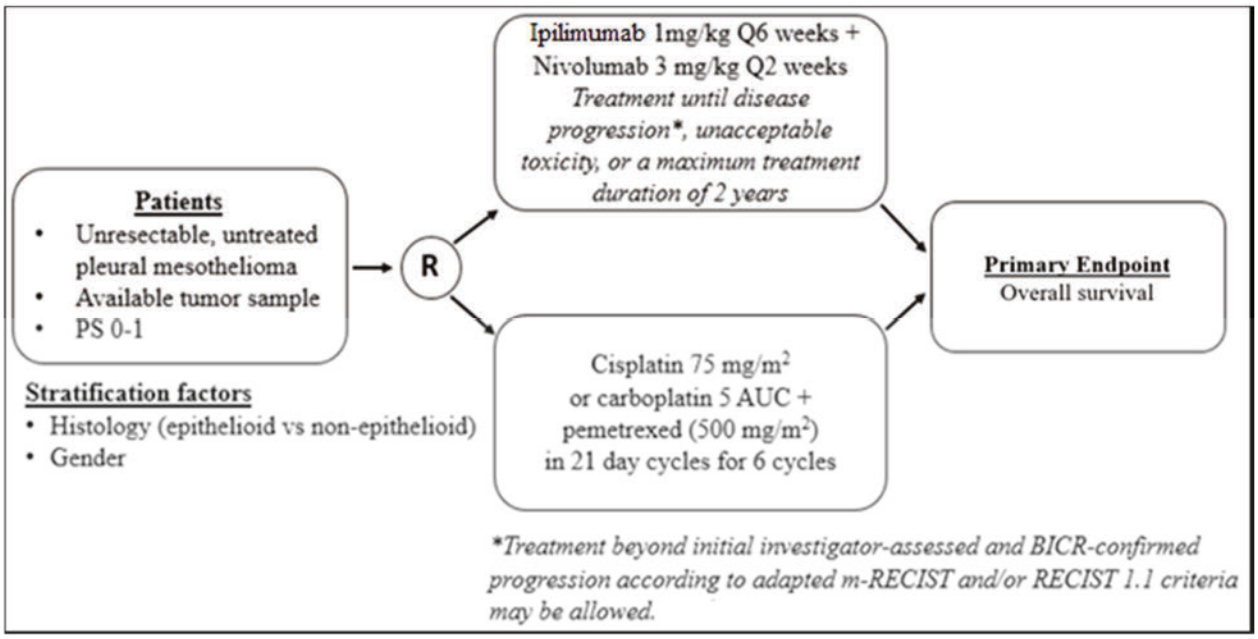
Randomization will be stratified according to tumor histology: Epithelioid vs non-epithelioid and sex: male vs female. Tumor sample for PD-L1 status assessment is required prior to randomization, but results are not needed for randomization.

Subjects will be treated with one of the following:

- Arm A (nivolumab/ipilimumab Combo): nivolumab 3 mg/kg IV every 2 weeks + ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable toxicity, or a maximum treatment duration of 2 years.
- Arm B (Control Arm): pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 or carboplatin (AUC of 5 mg per milliliter per minute), on day 1 of a 21-days cycle for 6 cycles or until disease progression or unacceptable toxicity. The choice of cisplatin is preferred, however the use of carboplatin is at the discretion of the investigator, and the reason for using carboplatin must be documented in the CRF. Arm B dose calculations will be administered according to label and/or local policy in terms of infusion schema (including but not limited to hydration protocols). Vitamins B12 and B9 supplementation and dexamethasone premedication are required for all subjects receiving pemetrexed. Dexamethasone can be given as IV infusion on the day of treatment as required by pemetrexed label and/or local SOC.

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

Figure 2.1-1: Study Design Schematic



2.2 Treatment Assignment

This is an open label, randomized, Phase 3 study in adult male and female subjects, as a first line therapy for diagnosed unresectable malignant pleural mesothelioma.

Subjects in each arm will be stratified by:

- histology: Epithelioid vs non-epithelioid
- sex: male or female

Subjects will be randomized in 1:1 and treated with one of open-label treatments Arm A or Arm B.

2.3 Blinding and Unblinding

This is an open label study. After participants are randomized, designated personnel of the Sponsor will have access to randomization assignment prior to database lock to facilitate data analysis.

[redacted]

[redacted]

2.5 Protocol Amendments

Table 2.5-1: Protocol Amendments

Document	Date of Issue	Summary of Changes
Revised Protocol 02	25-Apr-2019	• Change of progression free survival from co-primary to secondary endpoint and removal of hierarchical testing of secondary endpoints • Update of the statistical assumptions for the primary analysis in light of emerging data from external studies • Clarification of BICR assessed progression • Language updated for vaccines for prohibited treatment • Updated [redacted] • Updated adverse event definitions • Updated Appendix 2 [redacted] • Updated Appendix 3 Women of Child Bearing Potential Definition and Methods of Contraception

Table 2.5-1: Protocol Amendments

Document	Date of Issue	Summary of Changes
Revised Protocol 01	13-Oct-2017	• Addition of 2 year maximum treatment duration • Clarification of tissue submission requirements • Mesothelioma disease measurement updated • Radiographic assessment criteria of modified RECIST and RECIST 1.1 updated and imaging assessments were updated • Study design, assessments, and dosing schedule were clarified for consistency • Inclusion and exclusion criteria were updated • Language updated for prohibited treatments, treatment schedule, • Dose delay criteria for study treatment and discontinuation criteria were updated as per program standards [redacted] • Typographical and formatting errors were corrected and wording updated for consistency
Administrative Letter 06	07-Apr-2017	Incorporates clarifications on modified RECIST criteria in malignant pleural mesothelioma
Administrative Letter 05	06-Mar-2017	Updated study personnel and clarified treatment windows, pretreatment windows, and pathological tissue requirements. Chemotherapy treatment was updated for administration according to label and/or local policy and weight-based dosing calculations.
Administrative Letter 04	06-Dec-2016	Updated study personnel
Administrative Letter 03	27-Sep-2016	Prohibitions for the additional research collection and retention was clarified.
Administrative Letter 02	17-Aug-2016	Updated IND Number and updated chemotherapy infusion duration
Administrative Letter 01	20-Jul-2016	Updated title page information
Original Protocol	25-May-2016	Not applicable

* note other protocol amendments are site specific and did not require protocol to be updated.

2.6 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be utilized to provide general oversight and safety considerations for this study, CA209743. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit

profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety data for the study.

The DMC will be advisory to the clinical study leadership team. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

2.7 Blinded Independent Central Review (BICR)

A BICR will be employed for interpretation of radiographic progression events. At the time of investigator-assessed initial radiographic progression per adapted m-RECIST and/or RECIST 1.1 criteria in any given subject, the site must request the independent central review from the third party radiology vendor for confirmation of progression.

Tumor assessments for each subject should be submitted to the radiology vendor as they are performed on an ongoing basis. The blinded, independent radiologists will review all available tumor assessments for that given subject and determine if adapted m-RECIST and/or RECIST 1.1 criteria for progression have been met. The independent assessment of whether or not the given subject met criteria for progression will be provided to the site. Subjects whose disease progression is not confirmed centrally will be required to continue treatment and tumor assessments according to the protocol-specified schedule. Subsequent tumor assessments must be submitted to the third party radiology vendor for subsequent review and may be discontinued when the investigator and independent radiologists both assess the subject to have met criteria for progression.

The BICR will also review tumor images in all randomized subjects to determine adapted m-RECIST and/or RECIST 1.1 best overall response for the analyses of ORR.

At time of analysis of ORR, tumor assessments will use BICR in all randomized subjects to determine progression and response for the analyses of PFS and ORR. Details of the BICR responsibilities and procedures will be specified in the BICR charter.

3 OBJECTIVES

3.1 Primary Objectives

- To compare overall survival (OS) of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin regimen as first line treatment in subjects with unresectable malignant pleural mesothelioma.

3.2 Secondary Objectives

- To assess the objective response rate (ORR) as determined by Blinded Independent Committee Review (BICR), of nivolumab combined with ipilimumab and pemetrexed plus

cisplatin or carboplatin as first line treatment in subjects with unresectable pleural mesothelioma.

  - To assess the Disease Control Rate (DCR) as determined by BICR, of nivolumab combined with ipilimumab and pemetrexed plus cisplatin or carboplatin as first line treatment in subjects with unresectable malignant pleural mesothelioma.

- To assess progression-free survival (PFS) as determined by BICR of nivolumab combined with ipilimumab and pemetrexed plus cisplatin or carboplatin as first line treatment in subjects with unresectable malignant pleural mesothelioma.
- To evaluate whether PD-L1 expression is a predictive biomarker for ORR, PFS, and OS.

4 ENDPOINTS

4.1 Primary Endpoints

4.1.1 Overall Survival

Overall survival (OS) is defined as the time from randomization to the date of death from any cause. For subjects that are alive, their survival time will be censored at the date of last contact date (or "last known alive date"). Overall survival will be censored at the date of randomization for subjects who were randomized but had no follow-up.

Survival follow-up will be conducted every 3 months after subject's off-treatment date.

4.2 Secondary Endpoints

4.2.1 Objective Response Rate

Objective Response Rate (ORR) is defined as the number of randomized subjects who achieve a best response of complete response (CR) or partial response (PR) based on BICR assessments

(using adapted m-RECIST and/or RECIST v1.1 criteria) divided by the number of all randomized subjects. Best Overall Response (BOR) is defined as the best response, as determined by the BICR, recorded between the date of randomization and the date of objectively documented progression per adapted m-RECIST and/or RECIST v1.1 criteria or the date of subsequent therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. Confirmation of response is required at least 4 weeks after the initial response.

4.2.2 Time to Response

Time to Response (TTR) is defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by the BICR. TTR will be evaluated for responders (confirmed CR or PR) only.

4.2.3 Duration of Response

Duration of Response (DOR) is defined as the time between the date of first documented response (CR or PR) to the date of the first documented tumor progression as determined by the BICR (per adapted m-RECIST and/or RECIST v1.1 criteria), or death due to any cause, whichever occurs first. Subjects who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessments prior to initiation of the subsequent anticancer therapy. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who neither progress nor die, DOR will be censored on the date of their last evaluable tumor assessment. DOR will be evaluated for responders (confirmed CR or PR) only.

4.2.4 Disease Control Rate (DCR)

DCR is defined as the proportion of all randomized subjects whose BOR is either CR or PR or SD per adapted m-RECIST and/or RECIST 1.1 criteria as assessed by BICR.

4.2.5 Progression-Free Survival

Two definitions are used for analysis of Progression-Free Survival (PFS). The primary definition accounts for subsequent therapy by censoring at the last evaluable tumor assessment on or prior to the date of subsequent therapy. The secondary definition is irrespective of subsequent therapy and does not account for subsequent therapy.

Clinical deterioration in the absence of unequivocal evidence of progression (per adapted m-RECIST and/or RECIST v1.1 criteria) is not considered progression for purposes of determining PFS.

PFS rates at fixed time points T (e.g. 6 months, depending on the minimum follow-up) are defined as the probability that a subject has not progressed and is alive at time *T* following randomization.

The first on-study tumor assessment is scheduled to be conducted at 6 weeks (± 1 week) following randomization. Subsequent tumor assessments are scheduled every 6 weeks (± 1 week) up to 12 months, then every 12 weeks until disease progression.

4.2.5.1 Primary Definition of Progression-Free Survival (Accounting for Subsequent Therapy)

The primary definition of PFS (PFS truncated at subsequent therapy) is defined as the time between the date of randomization and the date of first documented tumor progression, based on BICR assessments (per adapted m-RECIST and/or RECIST v1.1 criteria), or death due to any cause, whichever occurs first. Figure 4.2.5.1-1: show the graphic display of primary definition of PFS.

Subjects who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the primary definition of PFS:

- 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 receive subsequent anti-cancer therapy prior to documented progression will be censored at the date of the last evaluable tumor assessment conducted on or prior to the date of initiation of the subsequent anti-cancer therapy.
- Subjects who did not have a documented progression and received subsequent anti-cancer therapy will be censored at the date of the last evaluable tumor assessment conducted on or prior to the initiation of the subsequent anti-cancer therapy.

Censoring rules for the primary definition of PFS (PFS truncated at subsequent therapy) are presented as follows and in Table 4.2.5.1-1.

Figure 4.2.5.1-1: PFS Primary Definition

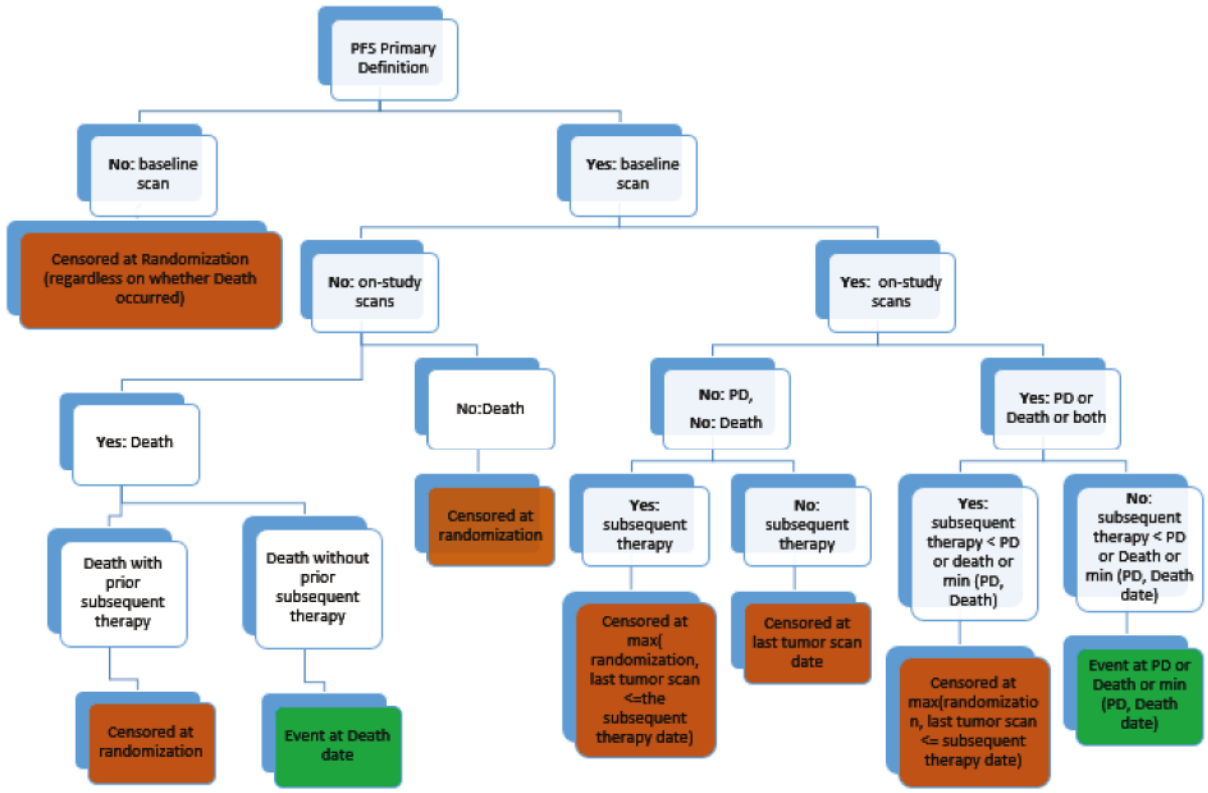


Table 4.2.5.1-1: Censoring Scheme Used in Primary Definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments*	Date of randomization	Censored
No on study tumor assessments and no death*	Date of randomization	Censored
Subsequent anti-cancer therapy started without death or progression per RECIST v1.1 reported prior or on the same day	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Documented progression per RECIST v1.1 and no new anti-cancer started before	Date of the first documented progression per RECIST v1.1 (excludes clinical progression)	Progressed
No progression and no death, and no new anti-cancer therapy started	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1 and no new anti-cancer started before	Date of death	Progressed

* Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered.

4.2.5.2 Secondary Definition of Progression Free Survival (Irrespective of Subsequent Therapy)

The secondary definition of PFS (ITT definition) is defined as the time between the date of randomization and the date of first documented tumor progression, based on BICR assessments (per adapted m-RECIST and/or RECIST v1.1 criteria), or death due to any cause, whichever occurs first. Figure 4.2.5.2-1: show the graphic display of secondary definition of PFS.

Subjects who die without a reported progression will be considered to have progressed on the date of their death. The following censoring rules will be applied for the secondary definition of PFS:

- 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.

Censoring rules for the secondary definition of PFS (ITT definition) are presented as follows and in Table 4.2.5.2-1.

Figure 4.2.5.2-1: PFS Secondary Definition

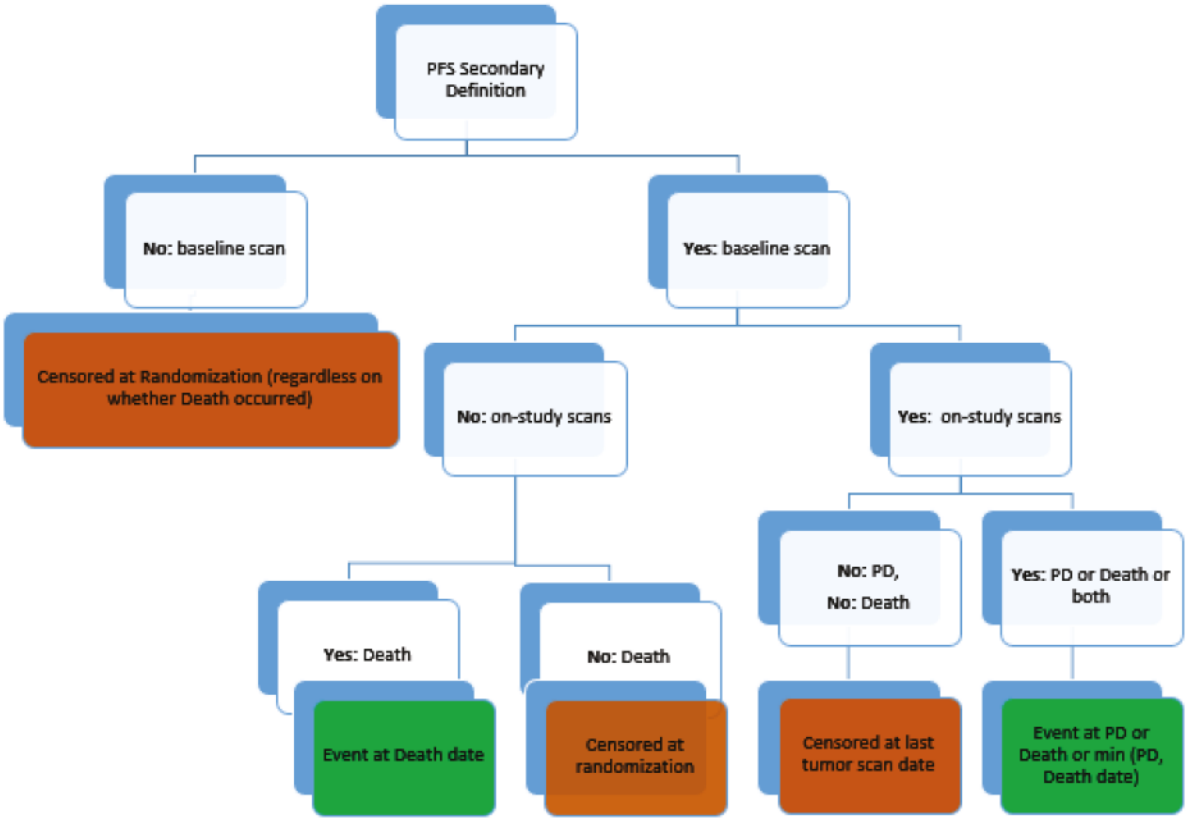


Table 4.2.5.2-1: Censoring Scheme for Secondary Definition of PFS

Situation	Date of Progression of Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression per RECIST v1.1	Date of first documented progression per RECIST v1.1 criteria (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1	Date of death	Progressed

4.2.6 PD-L1 Expression as a Predictive Biomarker for ORR, PFS, and OS

PD-L1 expression is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry (IHC) assay. This is referred to as quantifiable PD-L1 expression. If the PD-L1 staining could not be quantified, it is further classified as:

1) Indeterminate: Tumor cell membrane staining hampered for reasons attributed to the biology of the tumor tissue sample and not because of improper sample preparation or handling.
2) Not evaluable: Tumor tissue sample was not optimally collected or prepared and PD-L1 expression is neither quantifiable nor indeterminate. Not evaluable can be determined from H&E process before the tumor biopsy specimen is sent for PD-L1 evaluation or from the H&E process during PD-L1 evaluation.

Subjects with missing PD-L1 expression are subjects with no tumor tissue sample available for evaluation.

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

The study accounts for a primary endpoint: OS. Overall two-sided alpha (type I error rate) is set at 0.05 for evaluating OS. Approximately 600 patients were to be randomized with 1:1 ratio to two treatment arms with 606 subjects actually randomized. 473 OS events will be needed for the final analysis. The sample size is calculated to compare OS between nivolumab combined with ipilimumab (Arm A) and pemetrexed plus cisplatin or carboplatin regimen (Arm B). One formal interim analysis is planned for OS at 403 OS events. Table 5-1 summarizes the key parameters of trial design.

Overall survival: The key design parameters are shown in Table 5-1, where OS endpoint will utilize a group sequential design (GSD) with one interim analysis at 403 OS events and final analysis at 473 OS events. Stopping boundaries of GSD at the interim and final OS analyses will be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. Given accrual rate of 34 patients per month, it is estimated that it will take approximately 38/56 months to observe the required number of events for the interim/final OS analysis.

An exponential distribution is assumed for the OS time of control Arm B with a median OS time of 16 months and hazard rate of 0.043. To capture some observed features on the survival curves of immuno-therapies, a piecewise exponential models is assumed for the survival time on nivolumab plus ipilimumab arm. In particular, a piecewise exponential with hazard rates of 0.043, 0.033, and 0.0001 in the following post first dose time windows: first 6-month, 6 month to 34 month, and after 34 month, will provide a delay of treatment effect in the first 6 months, an exponential distribution of OS from 6 month to 34 month, and a long term survival rate plateau starting approximately at 34 month. Simulation evaluation of trial design show that the above piecewise

exponential distribution will produce a 90% power in log-rank test. The numerical value of type one error rate in simulation is 0.05.

The above sample size calculation was based on a simulation model incorporating aspects of immuno-oncology therapies like delayed separation and long term benefit using EAST 6.

Table 5-1: Summary of Key Design Parameters

Primary Endpoints	OS
Targeted Power	90%
Alpha	0.05 2-sided (0.03 at IA; 0.041 at FA)
Sample Size	606
Expected number of events for IA (percentage of target event)	403 (85%)
Target number of events	473
Duration (monthly accrual rate = 34 patients)	56 months

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

- Baseline period:
  - Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment. Evaluations (laboratory tests,) on the same date and time of the first dose of study treatment will be considered as baseline evaluations. Events (AEs) on the same date and time of the first dose of study treatment will not be considered as pre-treatment events.
  - 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) 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 on or prior to the first dose of study treatment:
    - For laboratory tests, the latest non missing labs value on or before first dose date (and time if collected) will be used as the baseline in the analyses. For 'LIPASE' and 'GLUCOSE', for treated subjects only, the last predose assessment with non-missing toxicity grade will be considered as baseline. If multiple assessments exist with the same collection date (and time if collected) and entry date and time, then the first observation is used as baseline.
    - For Eastern Cooperative Oncology Group (ECOG) performance status (PS), the latest ECOG PS value prior to or on the first dose date (and time if collected) will be used as

the baseline in the analyses. If multiple records fall on the last date then the record with the highest value of ECOG PS will be considered as baseline.

- For PD-L1, among the records prior to or on first dose date (and time if collected), identify first those with quantifiable test result. If there are no records with quantifiable test result, then select those with indeterminant result ("INDETERMINATE"). If there are no records with indeterminant test result, then select those with unavailable result ("NOT EVALUABLE). If there are no records with unavailable test result, then select those with not reported or not available result (all other records). The latest record will be used as the baseline in the analyses. If there is more than one record for the latest date, then choose the one with the greatest specimen ID.
- For Anti-Drug Antibody (ADA), the record related to the most recent assessment among those records where date (and time if collected) of nivolumab/ipilimumab immunoglobulin (IMG) assessment is less than or equal to the date (and time if collected) of the first nivolumab/ipilimumab dose date.

- Post baseline period:
  - On-treatment AEs will be defined as AEs with an onset date and time on or after the date and 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). For subjects who are off study treatment, AEs will be included if event occurred within a safety window of 100 days after the last dose of study treatment. No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.
  - On-treatment evaluations (laboratory tests) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, evaluations should be within a safety window of 100 days after the last dose of study treatment.
  - Late-emergent drug-related AEs will be defined as drug-related AEs with an onset date greater than 100 days after the last dose of study treatment in subjects who are off study treatment.

6.2 Treatment Regimens

Treatment group "as randomized" corresponds to the treatment group assigned by the Interactive Response Technology (IRT) system.

- Arm A: nivolumab 3 mg/kg IV every 2 weeks + ipilimumab 1 mg/kg IV every 6 weeks
- Arm B: pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 or carboplatin (AUC of 5 mg per milliliter per minute), on day 1 of a 21-days cycle for 6 cycles

The treatment group "as treated" will be same as the treatment group "as randomized" by IRT unless a subject received the incorrect study treatment for the entire period of treatment, in which case the subject's treatment group "as treated" will be defined as the incorrect study treatment.

Unless otherwise specified, the safety analysis will be based on the treatment group "as treated".

Unless otherwise specified, the efficacy analysis will be based on the treatment group "as randomized".

6.3 Populations for Analyses

- All Enrolled subjects: All subjects who signed the informed consent form and obtained a subject number.
- All Randomized subjects: All subjects who were randomized through the IRT.
- All Treated subjects: All randomized subjects who received at least one dose of any study treatment.
- Response-Evaluable Subjects: All randomized subjects with measurable disease at a baseline tumor assessment and at least one on-treatment tumor assessment.

[redacted]

- All PD-L1 Tested Subjects: Randomized 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
- All Treated, PD-L1 Tested Subjects: All PD-L1 tested subjects who received at least one dose of study treatment

Unless otherwise specified, the safety analyses will include all treated subjects.

Unless otherwise specified, the efficacy analyses will include all randomized subjects.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, discrete variables will be tabulated by the frequency and proportion of subjects falling into each category, grouped by treatment. Percentages given in these tables will be rounded to the first decimal and, therefore, may not always sum to 100%. Percentages less than 0.1 will be indicated as '< 0.1'. Continuous variables will be summarized by treatment group using the mean, standard deviation, median, minimum, and maximum values.

Time-to-event variables (e.g. time-to resolution) will be analyzed using the Kaplan-Meier technique. When specified, the median will be reported along with 95% CI using Brookmeyer and Crowley method[7] (using log-log transformation for constructing the confidence intervals[8]).

The conventions to be used for imputing missing and partial dates for analyses requiring dates are described in Section 8.

7.1.1 Adverse Events, Serious Adverse Events, Multiple Events, Select Adverse Events, Other Events of Special Interest and Immune-Mediated Adverse Events

Drug-related AEs are those events with relationship to study drug "Related", as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related.

Serious adverse events consist of AEs deemed serious by the Investigator and flagged accordingly in the CRF and clinical database.

Adverse events leading to study drug discontinuation are AEs with action taken regarding study drug(s) = "Drug was discontinued".

Adverse events leading to dose delay are AEs with action taken regarding study drug(s) = "Drug was delayed".

Adverse events leading to dose reduction are AEs with action taken regarding study drug(s) = "Dose was reduced".

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) and the most recent version of the criteria at the time of the database lock will be used.

In the AE summary tables, unless otherwise specified, subjects will be counted only once at the Preferred Term (PT), only once at the System Organ Class (SOC), and only once at subject level for the counting of total number of subjects with an AE. The AE tables will be sorted by the SOCs and then PTs. SOC will be ordered by descending frequency overall and then alphabetically. PTs will be ordered within SOC by descending frequency overall and then alphabetically. The sorting will be done based on the 'Any Grade' column of the experimental arm when arms are presented side-by-side.

Unless otherwise specified, the AE summary tables will be restricted to on-treatment events regardless of the causality.

Analyses that take into account the multiple occurrences of a given adverse event will be conducted (see Section 7.6.9). To prepare these analyses, the CRF data will be processed according to standard BMS algorithms[9] in order to collapse adverse event records into unique records based on the preferred term. These data will be presented as the rate per 100 person-years of exposure. These analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total exposure time. The person-year exposure will be computed as the sum over the subjects' exposure expressed in years where the exposure time is defined as

- (Date of last dose of study treatment - date of first dose of study treatment + 101 days)/365.25, for subject who are off study treatment and were followed for at least 30 days (or 100 days, depending on the analysis) after last dose of study treatment.

- (Last known alive date - date of first dose of study treatment +1)/365.25, for subjects who are still on-treatment or who are off study treatment and were followed less than 100 days after last dose of study treatment.

7.1.1.1 Select Adverse Events (EU Submission)

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (e.g. pulmonary events, gastrointestinal events categories, etc.). AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. Categories of select AEs may include subcategories (e.g. adrenal disorders, diabetes, pituitary disorders, and thyroid disorders are subcategories of the endocrine event category).

The list of MedDRA preferred terms used to identify select adverse events is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock will be provided by categories/subcategories.

In addition to the frequency and worst severity of select AEs, time-to onset, time-to resolution, and time-to resolution where immune modulating medication was initiated will be analyzed for each specific category/subcategory of drug-related select AEs when applicable.

Further details on the definitions of select adverse event, time-to onset and time-to resolution are described in APPENDIX 1.

7.1.1.2 Other Events of Special Interest

Other events of special interest (OEOSI) consist of a list of preferred terms grouped by specific category. The list of MedDRA preferred terms used to identify OEOSI is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.1.1.3 Immune-Mediated Adverse Events (US Submission)

In order to further characterize AEs of special clinical interest, analysis of immune-mediated AEs (IMAE) will be conducted. IMAEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator that meet the definition summarized below:

- those occurring within 100 days of the last dose,
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine AEs such as adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).

- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component

The list of MedDRA preferred terms used to identify IMAEs is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.1.2 Laboratory Tests

Clinical laboratory parameters (hematology, serum chemistry and electrolytes) will be evaluated.

Laboratory tests will be graded using the NCI Common Terminology Criteria, and the most recent version of the criteria at the time of the database lock will be used.

Clinical laboratory data will be first analyzed using International System of Units (SI). Analyses will be repeated using US conventional units.

In the laboratory summary tables, unless otherwise specified, subjects will be counted only once for each lab parameter according to their worst on treatment CTC grade (worst being the highest CTC grade). The laboratory tables and listings will be sorted by laboratory category, laboratory subcategory and laboratory test code sequence number.

[redacted]

7.2 Study Conduct

The following programmable deviations will be considered as relevant protocol deviations.

Eligibility:

- Subjects without measurable disease at baseline as per investigator
- Subjects with baseline ECOG PS>1
- Subjects who received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
- Subjects who received prior chemotherapy for pleural mesothelioma

On-study:

- Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of pleural mesothelioma) while on study therapy

- Subjects treated differently than as randomized (subjects who received the wrong treatment for the entire treatment period, excluding the never treated)

The Relevant Protocol Deviations will be summarized and listed based on all randomized subjects, by treatment group and overall.

Enrollment by country and site, and enrollment by month will be summarized and listed for all enrolled subjects.

A by-subject listing of batch numbers for all treated subjects will be provided.

7.3 Study Population

Analyses in this section will be tabulated for all randomized subjects by treatment group as randomized, unless otherwise specified.

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 subjects population only.

Number of subjects randomized but not treated along with the reason for not being treated will be tabulated by treatment group as randomized.

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 only on the all treated subjects population.

A by-subject listing for all treated subjects will be provided showing the subject's off treatment date and whether the subject continue in the treatment period/study along with the reason for going off treatment period/study. A by-subject listing for all enrolled subjects will also be provided, showing whether the subject was randomized/treated along with the reason for not being randomized/treated.

7.3.2 Demographics and Other Baseline Disease Characteristics

The following demographic and baseline disease characteristics will be summarized and listed by treatment group as randomized:

- Age (continuous)
- Age categorization (< 65, ≥ 65 and < 75, ≥ 75 and < 85, ≥ 85, ≥ 75, ≥ 65)
- Sex (Male vs. Female)
- Race (White, Black or African American, Asian, Other)
- Ethnicity (Hispanic/Latino and Not Hispanic/Latino)
- Country by geographic region
- Baseline ECOG performance status

- Tobacco use (Never, Former, Current, Unknown)
- Disease stage at study entry (Stage I, Stage II, Stage III, Stage IV)
- Time from initial disease diagnosis to randomization (< 1 year, ≥ 1 year)
- Baseline histology cell type (Epithelioid, Mixed, Sarcomatoid, Other)
- Sites of diseases (all lesions)
- Number of disease sites per subject (all lesions)
- Number of target lesions, non-target lesions and disease sites at baseline as per BICR
- Tumor burden: sum of the diameters of target lesions at baseline
- Region (North America, EU, Asia, Rest of World)

Summary table (cross-tabulation) by treatment group for stratification factor will be provided to show any discrepancies between what was reported through IRT vs. CRF at baseline. This summary will be performed based on all randomized subjects.

7.3.3 Medical History

A by-subject listing of general medical history for all randomized subjects will be provided.

7.3.4 Prior Therapy Agents

Prior cancer therapy will be summarized by treatment group and overall. Prior systemic cancer therapy will be summarized by treatment group and overall and listed by subject. Prior radiotherapy and prior surgery related to cancer will be listed by subject.

7.3.5 Physical Examinations

Subjects with abnormal baseline physical examination will be listed by subject.

7.3.6 Baseline Physical Measurements

Baseline physical measurements will be listed by subject.

7.3.7 Discrepancies between IVRS and CRF Stratification Factors

Summary tables (cross-tabulations) by treatment group for each stratification factor will be provided to show any discrepancies between what was reported through IVRS vs. CRF data (baseline).

7.4 Extent of Exposure

Listings will include all available exposure data. 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:

- Number of doses received
- Cumulative dose
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%

Duration of study therapy will be summarized (descriptive statistics) by treatment group.

A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose changes) will be also provided.

Table 7.4.1-1: Study Therapy Parameter Definitions- Nivolumab and Ipilimumab

	Nivolumab	Ipilimumab
Dosing schedule per protocol	3 mg/kg every 2 weeks	1 mg/kg every 6 weeks
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.
Cumulative Dose	*Cum dose (mg/kg) is* sum of the doses (mg/kg) administered to a subject.	*Cum dose (mg/kg) is* sum of the doses (mg/kg) administered to a subject.
Relative dose intensity (%)	Cum dose (mg/kg)/[(Last Nivolumab dose date - Nivolumab start dose date + 14) x 3/14] x 100	Cum dose (mg/kg)/[(Last Nivolumab dose date - Nivolumab start dose date + 42) x 1/42] x 100
Duration of treatment (overall)	Last Nivolumab dose date - Nivolumab start dose date +1	Last Ipilimumab dose date - Ipilimumab start dose date +1

Table 7.4.1-2: Study Therapy Parameter Definitions-Pemetrexed/Cisplatin

	Pemetrexed	Cisplatin
Dosing schedule per protocol	500 mg/ m^2 every 3 weeks	75mg/ m^2 every 3 weeks
Dose	*Dose (mg/m^2)* is defined as Total Dose administered (mg)/Most recent BSA. Dose administered in mg at each dosing date is collected on the CRF and BSA is derived from most recent weight and baseline height also collected on the CRF.	*Dose (mg/m^2)* is defined as Total Dose administered (mg)/Most recent BSA. Dose administered in mg at each dosing date is collected on the CRF and BSA is derived from most recent weight and baseline height also collected on the CRF.
Cumulative Dose	*Cum dose (mg/m^2) is* sum of the doses (mg/m^2) administered to a subject.	*Cum dose (mg/m^2) is* sum of the doses (mg/m^2) administered to a subject.

Table 7.4.1-2: Study Therapy Parameter Definitions-Pemetrexed/Cisplatin

	Pemetrexed	Cisplatin
Relative dose intensity (%)	Cum dose (mg/m²)/[(Last Pemetrexed dose date - Pemetrexed Start dose date + 21) x 500/21] x 100	Cum dose (mg/m²)/[(Last Cisplatin dose date - Cisplatin Start dose date + 21) x 75/21] x 100
Duration of treatment (overall)	Last dose date - Start dose date +1 (start dose date of the combination is the first date between the first dose dates of the two drugs of the combination and last dose date of the combination is the last date between the last dose dates of the two drugs of the combination)	Last dose date - Start dose date +1

Table 7.4.1-3: Study Therapy Parameter Definitions- Pemetrexed/Carboplatin

	Pemetrexed	Carboplatin
Dosing schedule per protocol	500mg/m² every 3 weeks	AUC 5 on day 1 of every 3 week cycle
Dose	*Dose (mg/m²)* is defined as Total Dose administered in mg at each dosing date is collected on the CRF and BSA is derived from most recent weight and baseline height also collected on the CRF.	*Dose (AUC)* is defined as Total Dose administered (mg)/(creatinine clearance +25). Dose administered in mg at each dosing date is collected on the CRF and creatinine clearance derived from the CRF data.
Cumulative Dose	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject.	*Cum dose (AUC) is* sum of the doses (AUC) administered to a subject.
Relative dose intensity (%)	Cum dose (mg/m²)/[(Last Pemetrexed dose date - Pemetrexed Start dose date + 21) x 500/21] x 100	Cum dose (AUC)/[(Last dose date of Carbo - Start dose date of Carbo + 21) x 5/21] x 100
Duration of treatment (overall)	Last dose date - Start dose date +1 (start dose date of the combination is the first date between the first dose dates of the two drugs of the combination and last dose date of the combination is the last date between the last dose dates of the two drugs of the combination)	Last dose date - Start dose date +1
Duration of treatment (maintenance)	Last Pemetrexed maintenance dose date- first Pemetrexed maintenance dose date + 1	

Table 7.4.1-3: Study Therapy Parameter Definitions- Pemetrexed/Carboplatin

	Pemetrexed	Carboplatin
Cumulative dose (maintenance)	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject in the maintenance phase.	

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 (i.e. greater than or equal to 4 days from scheduled dosing date) for nivolumab and ipilimumab. All study 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 subjects with at least one dose delayed, the number of dose delays per subject, the reason for dose delay and the length of dose 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, the reason for reduction and the number of infusion with IV rate reduction per subject.

7.4.2.3 Dose Escalations

Dose escalations (within subject) are not permitted for either nivolumab or ipilimumab.

7.4.2.4 Dose Reductions

Dose reductions (within subject) are not permitted for either nivolumab or ipilimumab. Dose of platinum doublet chemotherapy may be modified for toxicity. Dose levels of platinum doublet chemotherapy are defined in the protocol as follows:

Table 7.4.2.4-1: Dose Levels for Pemetrexed, Cisplatin, and Carboplatin

	Pemetrexed	Cisplatin	Carboplatin
Starting Dose	500 mg/m²	75 mg/m²	AUC 5.0
Dose Level -1	375 mg/m²	56 mg/m²	AUC 4.0
Dose Level -2	250 mg/m²	38 mg/m²	AUC 3.0
Dose Level -3	Stop drug	Stop drug	Stop drug

For any cycle, it will be defined as a dose reduction if the observed dose level (based on calculated administered dose) is below the dose level of the previously administered dose. Dose ranges for dose levels of platinum doublet chemotherapy are defined in Table 7.4.2.4-2.

Table 7.4.2.4-2: Calculated Dose Ranges and Related Dose Levels

Dose Level	Dose Range		
	Pemetrexed (mg/m²)	Cisplatin (mg/m²)	Carboplatin (AUC)
Level 0	≥437.5	≥65.5	≥4.5
Level -1	<437.5 and ≥312.5	<65.5 and ≥47	<4.5 and ≥3.5
Level -2	<312.5	<47	<3.5

The reason for dose reduction as reported by the investigator will be tabulated for all instances of dose reduction based on the Dose Change CRF page. A category 'Unknown' will be defined for all reductions with no reason reported by the investigator.

The following will be summarized for chemotherapeutic agent arm only:

- Number and percentage of subjects with at least one dose reduction and reason of the dose reduction, number and percentage of subjects with a dose reduction to dose level -1, number and percentage of subjects with a dose reduction to dose level -2.

7.4.2.5 Dose Omissions

Dose omissions are not permitted for either nivolumab or ipilimumab.

7.4.2.6 Partial Discontinuation of Ipilimumab in the Arm A

Subjects treated with nivolumab and ipilimumab may discontinue ipilimumab and continue to receive nivolumab (ie, partial discontinuation).

The following will be summarized for subjects receiving the immunotherapy in the arm A

- Number and percentage of subjects who had partial discontinuation of ipilimumab.
- Reason for partial discontinuation.

Reason for partial discontinuation will be retrieved from dosing CRF pages.

[redacted]

7.4.3.1 Immune Modulating Medication

Immune modulating concomitant medications are medications entered on an immune modulating medication form or available from the most current pre-defined list of immune modulating medications. The list of anatomic class, therapeutic class and generic name used for the selection at the time of the database lock will be provided.

The percentage of subjects who received immune modulating concomitant medication for

- management of adverse event
- premedication
- other use
- any use
- management of drug-related select adverse event (any grade, grade 3-5) by select AE category/ subcategory (EU Submission)
- management of IMAEs (any grade, grade 3-5) by IMAE category (US Submission) will be reported separately for each treatment group (percentages of treated subjects by medication class and generic term).

For each category/subcategory of drug-related select AEs (any grade, grade 3-5) and IMAEs (any grade, grade 3-5), the following will be reported for each treatment group:

- The total immune modulating medication treatment duration (excluding overlaps), duration of high dose of corticosteroid, initial dose of corticosteroid, and tapering duration (summary statistics)

Duration represents the total duration the subject received the concomitant medication of interest. If the subject took the medication periodically, then DURATION is the summation of all use. Initial dose represents the dose of the concomitant medication of interest received at the start of the event. In the case multiple medications started on the same date, the highest equivalent dose is chosen and converted to mg/kg by dividing by the subject's recent weight.

These analyses, except the ones related to IMAEs will be conducted using the 30-day safety window. The analyses related to IMAEs will be conducted using the 100-day safety window.

7.4.3.2 Subsequent Cancer Therapy

Number and percentage of subjects receiving subsequent cancer therapies will be summarized for all randomized subjects. Categories include:

- Subsequent systemic therapy
- Subsequent surgery for treatment of tumors
- Subsequent radiotherapy for treatment of tumors

A by-subject listing of subsequent cancer therapy will also be produced for all randomized subjects.

7.5 Efficacy

Principal analyses of progression free survival (PFS) and objective response rate (ORR) will be based on the Blinded Independent Central Review (BICR) evaluation, unless noted otherwise.

Analyses in this section will be tabulated for all randomized subjects by treatment group as randomized, unless otherwise specified.

Unless stated otherwise, whenever a stratified analysis is specified, the following stratifications factors (recorded at randomization as per IRT) will be used:

- Histology
- Sex

For assessing the secondary objectives of this study, no testing procedure will be used.

Confidence intervals (CI) for primary endpoint analyses will be based on nominal significance level adjusted for primary endpoints and interim analyses to preserve overall type one error rate.

Alpha (α) for the CI will be the same as nominal significance level for hypothesis testing. CIs for other endpoints will be at the two-sided 95% level. All p-values reported will be two-sided. P-values will be rounded to the fourth decimal place. Point estimates and confidence bounds for efficacy variables will be rounded to the second decimal place.

A by-subject listing of efficacy results will be presented including treatment group, treatment duration, BICR progression date, overall survival, death date, etc.

7.5.1 Analysis of Objective Response Rate

One of the objectives of the study is to estimate the ORR per BICR in the treatment groups among all randomized subjects.

The number and percentage of subjects in each category of BOR per BICR (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UTD]) will be presented, by treatment group. Estimates of response rate, along with its exact two-sided 95% CI by Clopper and Pearson[10] will be presented, by treatment group.

Similar analyses will be repeated based on the investigator's assessment of ORR. A cross tabulation of BICR best response versus the investigator best response will be presented, by treatment group and by response categories. Concordance Rate of Responders will be computed as the frequency with which investigator and BICR agree on classification of a subject as responder vs. non responder/UTD as a proportion of the total number of randomized subjects assessed by both the investigator and BICR.

The following subject-level graphics will also be provided:

- For the responders only, time courses of the following events of interest will be graphically displayed: tumor response.
- For response evaluable subjects (randomized subjects with baseline and at least one on-study tumor assessment),
  - A bar plot showing the best % reduction from baseline in sum of diameter of target lesions based on BICR assessment for each subject will be produced (excluding assessments after PD and assessments after start of subsequent anti-cancer therapy).
  - A plot of individual time course of tumor burden change per BICR assessment will be produced.

A by-subject listing of best overall response will be presented including treatment group, best overall response per BICR and dates of CR/PR/progression.

A by-subject listing of per time point tumor response per BICR will be presented.

7.5.2 Time to Tumor Response and Duration of Response

Duration of response (DOR) and time to response (TTR) will also be evaluated for subjects who achieved confirmed PR or CR. The DOR for each treatment group will be estimated using the

Kaplan-Meier (KM) product limit method and will be displayed graphically. A table will be produced presenting number of events, number of subjects involved, medians, and 95% CIs for the medians. Median values of DOR, along with two-sided 95% CI in each treatment group will be computed based on a log-log transformation method.

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

- Ongoing follow-up (current [last scan within adequate window vs cutoff date], not current)
- Off-study (lost to follow-up, withdraw consent, never treated)
- Received subsequent anticancer therapy.

TTR, which does not involve censoring, will be summarized by treatment group in all responders using descriptive statistics.

A by-subject listing will be presented including treatment group, best response, time to response, duration of response, whether the subject was censored for duration of response, and, if so, the reason.

7.5.3 Analysis of DCR

Similar to ORR analysis, BICR-determined DCR in arm A and B will be estimated and its corresponding 95% exact two-sided CIs will be calculated using the Clopper Pearson method. This analysis will also be performed for DCR as assessed by the investigators.

7.5.4 Analysis of Progression-Free Survival

The PFS function (as determined by BICR) for each treatment group will be estimated using the KM product limit method and will be displayed graphically. A two-sided 95% CI for median PFS in each treatment group will be computed via the log-log transformation method. PFS rates at fixed time points (e.g. 6 months, depending on the minimum follow-up) will be presented along with their associated 95% CIs. These estimates will be derived from the Kaplan Meier estimate and corresponding CIs will be derived based on Greenwood[11] formula for variance derivation and on log-log transformation applied on the survivor function[12].

Analyses of PFS (as determined by BICR) will be conducted based on the primary definition and secondary definition of PFS.

The source of PFS event (progression or death) will be summarized by treatment group. The status of subjects who are censored (as per primary definition of PFS) in the PFS KM analysis will be tabulated for each treatment group including the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdraw consent, never treated)
- No baseline tumor assessment
- No on-study tumor assessment and no death

- Received subsequent anticancer therapy

A by-subject listing will be presented including treatment group, PFS duration under the primary definition, PFS duration on the ITT definition, whether the subject was censored under the primary definition, and if censored, the reason, and whether the subject was censored under the ITT definition, and if censored, the reason.

A by-subject listing of lesion evaluations per BICR will be presented.

7.5.6 *Analysis of Overall Survival*

The primary objective of the study is to compare the overall survival between treatment groups in all randomized subjects.

Overall survival will be compared between the treatment groups at the interim and final analyses, using a stratified log-rank test. The stratification factors will be histology and sex. An O'Brien and Fleming α-spending function will be employed to determine the nominal significance levels for the interim and final analyses. The stratified hazard ratio between the treatment groups will be presented along with 100*(1- α)% CI (adjusted for interim). In addition, two-sided p-value will also be reported for the analysis of OS.

OS will be estimated using the KM techniques. A two-sided 95% CI for median OS in each treatment group will be computed via the log-log transformation method. OS rates at fixed time points (e.g. 6 months, depending on the minimum follow-up) will be presented along with their associated 95% CIs. These estimates will be derived from the Kaplan Meier estimate and corresponding CIs will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

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

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdraw consent, never treated)

A by-subject listing will be presented including treatment group, first and last dose date, whether the subject died, and if censored, the reason, event/censored date and OS duration.

[redacted]

[redacted]

7.5.8 Subset Analyses of Overall Survival

The influence of baseline and demographic characteristics on the treatment effect among all randomized subjects will be explored via exploratory subset analyses. The median OS based on KM product-limit method along with two-sided 95% CIs will be produced for the following subgroups:

- Age categorization (<65 vs.>=65 vs. ≥65-<75 vs >=75)
- Sex (Male vs. Female)
- Race (White, Black, Asian, Others)
- Region (North America vs. EU vs. Asia vs. ROW)
- ECOG performance status(0, ≥1)
- Baseline Histology (Epithelioid, Mixed, Sarcomatoid, Other)
- Disease stage at study entry (Stage I, Stage II, Stage III, Stage IV)
- Tobacco use (Never, Former, Current, Unknown)
- Prior radiotherapy (yes/no)
- Prior systemic cancer therapy (yes/no)
- PD-L1 (Positive, Negative)

A forest plot of the OS hazard ratios (along with the 95% CIs) will be produced for each level of the subgroups listed above. The HR for each forest plot will be calculated based on an unstratified Cox proportional hazards model.

An analysis will be conducted if the number of subjects in the subgroup category is more than 10.

7.5.9 Current Status of PFS and OS Follow-up

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

The currentness of follow-up for survival, defined as the time between last OS contact (i.e., last known alive date or death date) and cutoff date (defined by last patient last visit date), will be summarized in months for all randomized subjects. Subjects who died and subjects with last known alive date on or after data cut-off date will have zero value for currentness of follow-up.

Minimum follow-up for OS, defined as the time from cutoff date to last subject's randomization date, will be summarized in months for all randomized subjects.

Time from last evaluable tumor assessment to cutoff date in months will be summarized by treatment group and overall for all randomized subjects. Subjects who have a PFS event will be considered as current for this analysis. The secondary definition of PFS will be used for this summary.

In addition, time to treatment discontinuation will be summarized and 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 study therapy and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date.

A by-subject listing will also be produced to accompany the subject time from last evaluable tumor assessment.

7.5.10 Interim Analysis of Overall Survival

An independent statistician external to BMS will perform the analysis. In addition to the formal planned interim analysis for OS, the Data Monitoring Committee (DMC) will have access to periodic un-blinded interim reports of efficacy and safety to allow a risk/benefit assessment. Details are included in the DMC charter.

A formal interim analysis for superiority of OS in subjects who were randomized to Arm A vs. subjects who were randomized to Arm B will be performed on all randomized subjects when approximately 403 deaths have been observed (approximately 85% (403/473) of the total number of deaths required for the final analysis).

This OS comparison will be tested using the interim monitoring feature of EAST software based on a generalization of the Lan-DeMets Alpha spending function approach using an O'Brien-Fleming stopping boundary to reject H_0, controlling for a two-sided overall α of 5%. For example, if exactly 403 deaths are in the locked database at the interim analysis, H_0 would be rejected if the p-value from the log-rank test is $p < 0.03$. If the number of deaths is not exactly 403 at the time of the interim analysis, the nominal critical point and value of both the interim and final analyses will be calculated based upon the observed information fraction.

If the study continues beyond the interim analysis and exactly 403 deaths at the interim analysis and exactly 473 deaths are in the locked database at the final analysis, H_0 would be rejected if the p-value from the log-rank test is $p < 0.041$. All events in the database at the time of the lock will be used. The final analysis will be conducted after at least 473 deaths occurs.

The DMC will review the safety and efficacy data from the informal interim analyses and will determine if the study should continue with or without changes or if accrual should be stopped. Subject enrollment will continue while waiting for the DMC's decisions.

The chair of the DMC and the sponsor can call an unscheduled review of the safety data.

At the time of the formal interim analysis for superiority of OS, the DMC may recommend continuing or stopping the trial. If the trial continues beyond the formal interim analysis, the nominal critical point for the final OS analysis will be determined using the recalculated information fraction at the time of the interim analysis, as described above. The final OS hazard ratio and corresponding confidence interval will be reported whereby the confidence interval will be adjusted accordingly (i.e. using the recalculated nominal α level at the final analysis).

If the trial is stopped for superiority of OS at the interim, the p-value from the interim stratified log-rank test will be considered the final primary analysis result.

7.6 Safety

Analyses in this section will be tabulated for all treated subjects by treatment group as treated, unless otherwise specified.

7.6.1 Deaths

Deaths will be summarized by treatment group:

- All deaths, reasons for death.
- Deaths within 30 days of last dose received, reasons for death.
- Deaths within 100 days of last dose received, reasons for death.

A by-subject listing of deaths will be provided for the all enrolled subjects population.

7.6.2 Serious Adverse Events

Serious adverse events will be summarized by treatment group:

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

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

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

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation will be summarized by treatment group:

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

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

A by-subject AEs leading to discontinuation listing will be provided.

7.6.4 Adverse Events Leading to Dose Modification

AEs leading to dose delay/reduction will be summarized by treatment group:

- Overall summary of AEs leading to dose delay/reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of related AEs leading to dose delay/reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

The analysis will be conducted using the 30-day safety window.

A by-subject AEs leading to dose delay/reduction listing will be provided.

7.6.5 Adverse Events

Adverse events will be summarized by treatment group.

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

- Overall summary of any AEs by worst CTC grade (1, 2, 3, 4, 5, not reported, total) presented by SOC/PT.
- Overall summary of any AEs presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in any treatment group.
- Overall summary of any non-serious AEs presented by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in any treatment group.
- Overall summary of any AEs that required immune modulating medication by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related AEs by worst CTC grade (1, 2, 3, 4, 5, not reported, total) presented by SOC/PT.

The following analyses will be conducted using the 30 days safety window and repeated using the 100 days safety window:

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

A by-subject AE listing will be provided. A by-subject listing of any AE requiring immune modulating medications will also be provided.

7.6.6 Select Adverse Events (EU Submission)

Unless otherwise specified, analyses will be performed by select AE category. Analyses will also be repeated by subcategory of endocrine events.

7.6.6.1 Incidence of Select AE

Select AEs will be summarized by treatment group for each category/subcategory.

The following analyses will be conducted using the 30-day safety window only:

- Overall summaries of any select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT.
- Overall summaries of any drug-related select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT.

- Overall summaries of any serious select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of drug-related serious select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of any select AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Overall summaries of drug-related select AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory /PT.
- Summary of frequency of unique select AEs by Category.

A by-subject select AE listing will be provided.

7.6.6.2 Time-to Onset of Select AE

Time-to onset of drug-related select AEs (any grade, grade 3-5) will be summarized for each category/subcategory by treatment group.

Time-to onset analyses are restricted to treated subjects who experienced at least one drug-related select AE in the category/subcategory. The analyses will be conducted using the 30-day safety window.

Additional details regarding the time-to onset definition are described in time-to onset definition subsection of APPENDIX 1.

7.6.6.3 Time-to Resolution of Select AE

Time-to resolution of the following specific events will be summarized separately for each category/subcategory.

- Time-to resolution of drug-related select AE (any grade, grade 3-5) by treatment group
- Time-to resolution of drug-related select AE (any grade, grade 3-5) where immune modulating medication was initiated, by treatment group

Time-to resolution analyses are restricted to treated subjects who experienced the specific events. Time-to resolution where immune modulating medication was initiated analyses are restricted to treated subjects who experienced the specific events and who received immune modulating medication during the longest select AE.

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

The following summary statistics will be reported: percentage of subjects with resolution of the longest select AE, median time-to resolution along with 95% CI (derived from Kaplan-Meier estimation) and ranges.

See time-to resolution definition subsection of APPENDIX 1 for additional details.

7.6.7 Immune-Mediated Adverse Events (US Submission)

IMAEs will be summarized by treatment group for each immune-mediated category / PT using the 100-day safety window:

- Overall summary of non-endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT.
- Overall summary of endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT.
- Overall summary of non-endocrine IMAEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT.
- Overall summary of endocrine IMAEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT.
- Overall summary of non-endocrine IMAEs leading to dose delay or reduction by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT
- Overall summary of endocrine IMAEs leading to dose delay or reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT.
- Summaries of time-to onset and time-to resolution of non-endocrine IMAEs where immune modulating medication was initiated presented by Category.
- Summaries of time-to onset and time-to resolution of endocrine IMAEs presented by Category.

A by-subject listing of IMAEs will be provided. By-subject listings of time-to resolution for longest IMAEs cluster (any grade and grade 3-5 in separate summaries) will also be provided. For new studies which collect investigator assessment of potential IMAE data, a by-subject listing of AEs considered as immune-mediated events per investigator but not qualified for IMAEs definition will also be provided.

In addition, for all nivolumab treated subjects who experienced at least one IMAE, the following data presentation will be provided:

- Summary of subjects who were re-challenged with nivolumab by IMAE category, with extended follow-up
- Summary of subjects who were re-challenged with nivolumab or ipilimumab by IMAE category, with extended follow-up

For these, re-challenge is considered to have occurred when last nivolumab and/or ipilimumab infusion was administered after the onset of an IMAE.

7.6.8 Other Events of Special Interest

OEOSI will be summarized by treatment group for each category.

The following analyses will be conducted using the 100-day safety window:

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

A by-subject listing of OEOSI will be provided.

7.6.9 Multiple Events

The following summary tables will be provided:

- A table showing the total number and rate (exposure adjusted) of occurrences for all AEs.
- A table showing the total number and rate (exposure adjusted) of occurrences for AEs occurring in at least 5% of subjects in any treatment group.

In addition, the rate (exposure adjusted) and its 95% CI evaluated for different time intervals will be displayed graphically for each treatment group. This analysis will be limited to the rate of all AEs and all drug-related AEs. The analyses will be conducted using the 30-day safety window.

A listing displaying the unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e. same PT) have been collapsed will be provided. No formal comparisons will be made between treatment groups.

7.6.10 Laboratory Parameters

The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test. Laboratory tests (in addition to the tests specified below) with CTC criteria collected in the specific studies may also be included in the summaries.

7.6.10.1 Hematology

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: hemoglobin (HB), platelets, white blood counts (WBC), absolute neutrophils count (ANC) and lymphocyte count (LYMPH).

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

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

7.6.10.2 Serum Chemistry

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: ALT, AST, alkaline phosphatase (ALP), total bilirubin and creatinine.

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

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

7.6.10.3 Electrolytes

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: sodium (high and low), potassium (high and low), calcium (high and low), magnesium (high and low), and Glucose Serum (fasting hyperglycemia and hypoglycemia regardless of fasting status)

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

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

7.6.10.4 Additional Analyses

In addition, further analyses on specific laboratory parameters will be performed by treatment group:

Abnormal Hepatic Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

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

A by-subject listing of these specific abnormalities will be provided.

Abnormal Thyroid Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group:

- TSH value > ULN and
  - with baseline TSH value ≤ ULN
  - with at least one FT3/FT4 test value < LLN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≥ LLN within 2-week window after the abnormal TSH test
  - with FT3/FT4 missing within 2-week window after the abnormal TSH test.
- TSH < LLN and
  - with baseline TSH value ≥ LLN

- with at least one FT3/FT4 test value > ULN within 2-week window after the abnormal TSH test
- with all FT3/FT4 test values ≤ ULN within 2-week window after the abnormal TSH test
- with FT3/FT4 missing within 2-week window after the abnormal TSH test

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

A by-subject listing of these specific abnormalities will be provided.

7.6.11 Physical Measurements

Physical measurements will be listed by subject.

7.6.12 Non-Protocol Medical Procedures

Non-protocol medical procedures will be listed by subject.

[redacted]

7.6.14 Pregnancy

A by-subject listing of pregnancy tests results will be provided for randomized female subjects.

7.6.15 Adverse Events By Subgroup

Overall summary of any AEs and drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT and for each treatment group for the following subgroups:

- Sex (Male vs. Female)
- Race
- Age (< 65 vs. 65 - < 75 vs. 75 - < 85 vs. ≥ 85 vs. ≥ 75 vs. ≥ 65)
- Region (North America vs. EU vs. Asia vs. ROW)

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

[redacted]

7.8 Biomarkers

Analyses for PD-L1 are described below.

[redacted]

7.8.2 Association Between PD-L1 Expression and Efficacy

Analyses of association between PD-L1 expression at baseline and efficacy measures will be performed for scheduled formal efficacy analyses in the study. The analysis population will be among all randomized subjects unless otherwise specified.

For each PD-L1 subgroup (will be specified in the DPP) at baseline:

- OS/PFS curves for each treatment group will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median OS/PFS will be constructed based on a log-log transformed CI for the survivor function S(t).
- Forest plot of Hazard Ratios with 95% CIs
- Frequency and percentage of BOR per BICR will be summarized for each treatment group.
- ORR will be computed by treatment group along with exact 95% CIs using the Clopper Pearson method.

The following analysis will be performed to evaluate the association between PD-L1 expression level and BICR-determined PFS (per primary definition) or OS.

- An exploratory Cox proportional hazards model will be fitted for PFS per BICR or OS with PD-L1, treatment arm and PD-L1 treatment arm interaction, among All PD-L1 Evaluable Subjects. An appropriate transformation of PD-L1 expression may be considered depending on an assessment of fit of the model.
- A plot of estimated log(hazard ratio) with 95% confidence band vs PD-L1+ expression(X-axis)

The following analysis will be performed to evaluate the evaluation of association between PD-L1 expression level and ORR (per BICR) among PD-L1 evaluable subjects for each treatment arm.

- A logistic regression model will be fitted for ORR with PD-L1 among all PD-L1 evaluable subjects. An appropriate transformation of PD-L1 expression may be considered depending on an assessment of fit of the model.
- A plot of estimated response probability with 95% confidence band vs PD-L1 expression (X-axis)

- Box plot of PD-L1 expression versus Response Status

Receiver Operating Characteristics (ROC) analysis with ORR (per BICR) will be performed to help assess in-study predictive accuracy of the logistic regression model and whether there is a clinically meaningful threshold of PD-L1 Expression. A plot of the ROC curve and a plot of estimated Youden's index vs PD-L1 will be provided for all PD-L1 evaluable subjects.

[redacted]

[redacted]

8 CONVENTIONS

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

- For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[13]
- For missing and partial adverse event resolution dates, imputation will be performed as follows:
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day. If the imputed date is after the death date or the last known alive date, then the latest known alive date or death date is considered as the resolution date.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- Missing and partial non-study medication domain dates will be imputed using the derivation algorithm described in 4.1.3 of BMS Non-Study Medication Domain Requirements Specification[14].
- Missing and partial radiotherapy and surgery dates will be imputed using algorithm described in APPENDIX 2.
- 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 alive date 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 alive date.
  - 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 after start of study therapy, 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. In case of 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.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- For date of progression to prior therapies, 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.
- For other partial/missing dates, the following conventions were 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-to onset, time-to resolution) will be calculated as follows:

Duration = (Last date - first date + 1)

Last known alive date will be defined based on all appropriate dates collected on the CRF.

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

9 CONTENT OF REPORTS

All analyses describe in this SAP will be included in the final Clinical Study Report. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	[redacted]	Description
1.0		Original Version
1.1		Removed the protocol deviations that are challenging to program from the programmable protocol deviation list

APPENDIX 1 TIME-TO ONSET AND TIME-TO RESOLUTION DEFINITION AND CONVENTIONS FOR SELECT ADVERSE EVENTS, IMMUNE-MEDIATED ADVERSE EVENTS AND EVENTS OF SPECIAL INTEREST

Time-to onset definition

Time-to onset of AE (any grade) for a specific category is defined as the time between the day of the first dose of study treatment and the onset date of the earliest AE (of any grade) in this category.

The time-to onset of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to onset of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

Time-to onset for a specific subcategory is defined similarly but restricted to event of this subcategory.

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous AEs within a specific category or subcategory will be collapsed into what will be termed "clustered" AEs. For example, if a subject (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered AE from 1st to 12th January. Appendix Table 1 is summarizing key derivation steps for each type of clustered AEs.

Time-to resolution of AE (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered AEs experienced by the subject in this category per adverse event criteria category. Events which worsened into grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AE is considered as unresolved, the resolution date will be censored to the last known alive date. Improvement to the grade at baseline implies that all different events in the clustered adverse event should at least have improved to the corresponding (i.e. with same preferred term) baseline grade. This measure is defined only for subjects who experienced at least one AE in the specific category.

The time-to resolution of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to resolution of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

The time-to resolution of AE (any grade or grade 3-5, drug-related or all) where immune modulating medication was initiated is defined similarly. For data presentation not restricted to IMAE, the additional condition that the subject started an immune modulating medication during the longest AE resolution period will be applied.

Time-to resolution for a specific subcategory is defined similarly but restricted to event of this subcategory.

Appendix Table 1: Derivation of Clustered AE

Type of clustered AE	Derivation
Any grade	Collapse any on-treatment AE from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AE from the same category
Grade 3-5	Collapse any on-treatment AE from the same category. Resolution will be based on the onset date of the earliest grade 3-5 records (if no grade 3-5 record, clustered AE is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AE from the same category Resolution will be based on the onset date of the earliest grade 3-5 record (if no Grade 3-5 record, clustered AE is excluded)

[redacted]