

Statistical Analysis Plan for

Official Title of Study

**MULTICENTER, DOUBLE-BLIND, PHASE 3 STUDY OF NIVOLUMAB, NIVOLUMAB  
IN COMBINATION WITH IPILIMUMAB, OR PLACEBO AS MAINTENANCE  
THERAPY IN SUBJECTS WITH EXTENSIVE-STAGE DISEASE SMALL CELL LUNG  
CANCER (ED-SCLC) AFTER COMPLETION OF PLATINUM-BASED FIRST LINE  
CHEMOTHERAPY**

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**STATISTICAL ANALYSIS PLAN  
FOR CLINICAL STUDY REPORT**

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CHEMOTHERAPY**

**PROTOCOL(S) CA209-451**

**VERSION # 2.0**

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## 2 STUDY DESCRIPTION

### 2.1 Study Design

This is a randomized, double-blind, three-arm, multicenter, Phase 3 study in adult subjects with ED-SCLC, who achieve Stable Disease, Partial Response or Complete Response after completion of platinum based first line chemotherapy.

Approximately 810 subjects (see note below) will be randomized in a 1:1:1 ratio to treatment with either nivolumab monotherapy (Arm A), nivolumab/ipilimumab combination therapy (Arm B), or placebo (Arm C), and will be stratified according to the following factors:

- ECOG Performance Status: 0 vs. 1
- Sex: Male vs. Female
- Prophylactic Cranial Irradiation (PCI) following chemotherapy: Yes vs. No

The treatment arms are as follows:

- **Arm A:**
  - Nivolumab 240mg administered every 2 weeks as a 30min IV infusion, as described in [Table 2.1-1](#) and [Table 2.1-2](#).
- **Arm B:**
  - Nivolumab 1mg/kg (30min IV infusion) and ipilimumab 3mg/kg (90min IV infusion) every 3 weeks for four doses, followed by nivolumab 240mg every 2 weeks, as described in [Table 2.1-1](#) and [Table 2.1-2](#).
- **Arm C:**
  - Placebo administered as described in [Table 2.1-1](#) and [Table 2.1-2](#).

This study includes a sub-study in China to allow enrollment of patients from China. Approximately 70 additional subjects will be randomized from China.

In order to maintain a blinded study, the schedule of investigational and placebo treatments is divided into two 6-week cycles at the start of therapy, followed by ongoing 2-week cycles until discontinuation criteria are met. This schedule is described in [Table 2.1-1](#) and [Table 2.1-2](#).

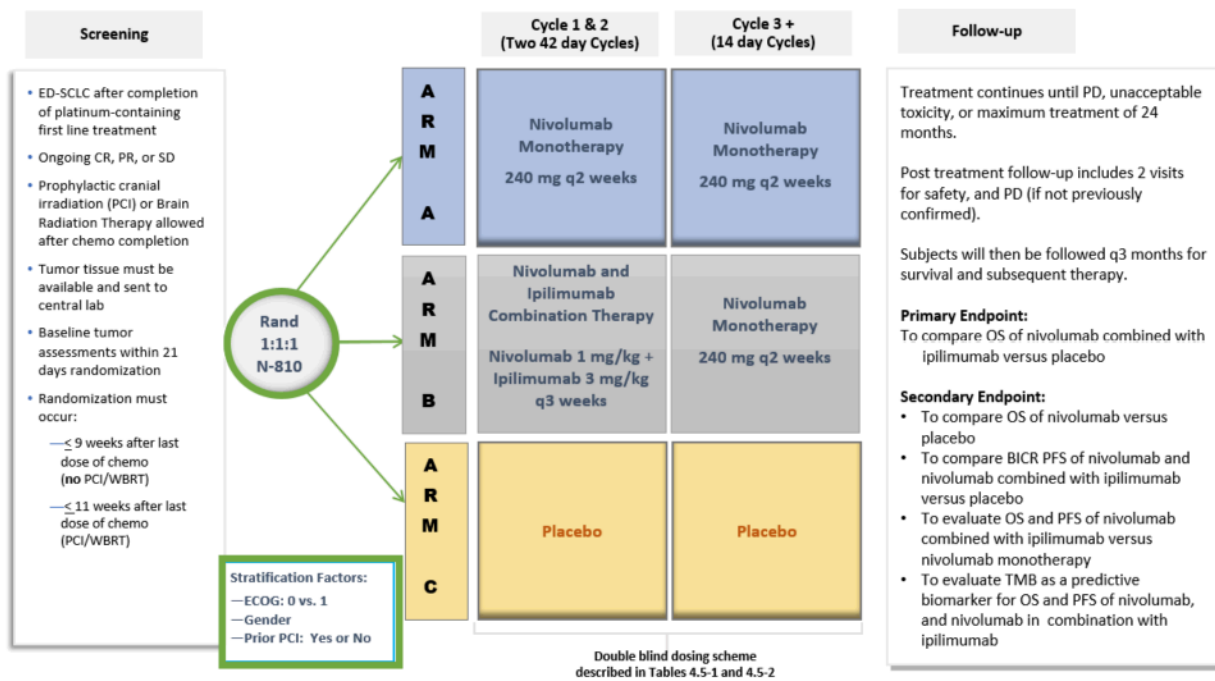
On-study tumor assessments will be conducted every 6 weeks ( $\pm 5$  days) for the first 36 weeks. After Week 36, tumor assessments will be performed every 12 weeks ( $\pm 5$  days) until disease progression.

Survival follow-up may continue for up to 5 years from the primary analysis of survival. The study will end once survival follow-up has concluded.

A BMS Medical Safety Team (MST) routinely reviews safety signals across the nivolumab program.

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

**Figure 2.1-1: Study Design Schematic**



The dosing schedule is detailed in Table 2.1-1 and Table 2.1-2

**Table 2.1-1: Blinded Dosing Schedule (Cycles 1 and 2)**

1 Cycle = 42 Days = 6 weeks						
	C1D1	C1D8	C1D15	C1D22	C1D29	C1D36
Arm A (Nivo)	Nivo: 240mg (24mL diluted to 100mL)  Ipi pbo: 100mL		Nivo: 240mg (24mL diluted to 100mL)	Nivo pbo: 100mL  Ipi pbo: 100mL	Nivo: 240mg (24mL diluted to 100mL)	
Arm B (Nivo + Ipi)	Nivo: 1mg/kg (diluted to 100mL)  Ipi: 3mg/kg (diluted to 100mL)		Nivo pbo: 100mL	Nivo: 1mg/kg (diluted to 100mL)  Ipi: 3mg/kg (diluted to 100mL)	Nivo pbo: 100mL	
Arm C (Placebo)	Nivo pbo: 100mL  Ipi pbo: 100mL		Nivo pbo: 100mL	Nivo pbo: 100mL  Ipi pbo: 100mL	Nivo pbo: 100mL	x

**Table 2.1-2: Blinded Dosing Schedule (Cycle 3+)**

1 Cycle = 14 Days = 2 weeks		
	C3D1	C3D8
Arm A (Nivo)	Nivo: 240mg (24mL diluted to 100mL)	
Arm B (Nivo + Ipi)	Nivo: 240mg (24mL diluted to 100mL)	
Arm C (Placebo)	Nivo pbo: 100mL	

## 2.2 Treatment Assignment

Subjects are enrolled using the Interactive Voice Response System (IVRS) to obtain a subject ID. Subjects who have signed informed consent and met all eligibility criteria will be ready to be randomized through the IVRS, upon confirmation of receipt of required tissue sample by the central lab. The following information is required for subject randomization:

- Subject number
- Date of birth
- Submission of tumor tissue sample to central lab
- ECOG Performance Status: 0 vs. 1
- Sex: Male vs. Female
- Prophylactic Cranial Irradiation (PCI) following chemotherapy: Yes vs. No

The IVRS will randomly assign the subject in a 1:1:1 ratio to either Arm A (nivolumab), Arm B (nivolumab/ ipilimumab), or Arm C (placebo), stratified by the following factors:

- ECOG Performance Status: 0 vs. 1
- Sex: Male vs. Female
- Prophylactic Cranial Irradiation (PCI) following chemotherapy: Yes vs. No

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

## 2.3 Blinding and Unblinding

The subjects, investigator and site staff will be blinded to the study drug administered. Each investigative site must assign an unblinded pharmacist. An unblinded site monitor will be assigned by the Sponsor/or designee to provide oversight of drug supply and other unblinded study documentation. In the event of a medical emergency in an individual subject, the treating physician may be unblinded if knowledge of the investigational product is critical to the subject's management.

The Sponsor will remain blinded until final PFS results are unblinded following guidelines specified in the DMC Charter or until final analysis of the OS endpoint, whichever occurs first. The independent DMC will be unblinded to enable review of safety and efficacy reports. Details are specified in the DMC Charter

Designated staff of BMS Research & Development may be unblinded prior to database lock to facilitate bioanalytical analyses. A bioanalytical scientist in the Bioanalytical Sciences department (or designee in the external central bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples from control group subjects.

## 2.4 Protocol Amendments

**Table 2.4-1: Protocol Amendments**

Amendments	Date of issue	Summary of Major Changes
Revised Protocol 06	20-Sep-2018	<ul style="list-style-type: none"> <li>Moved OS of nivolumab vs placebo to secondary objectives</li> <li>Updated sample size and power analysis</li> </ul>
Revised Protocol 05	14-Jul-2018	<ul style="list-style-type: none"> <li>BICR-assessed PFS was changed from primary objective to secondary objective and the associated PFS analysis was removed</li> <li>To evaluate Tumor mutational burden (TMB) as a potential predictive biomarker for efficacy was added as secondary objective</li> <li>The number of events required for primary analysis of OS was changed from 576 events to 593 events</li> </ul>
Revised Protocol 04	12-Sep-2017	<ul style="list-style-type: none"> <li>Details of tissue requirements updated</li> <li>Maximum treatment duration added</li> <li>Contraception language updated to program standards</li> <li>Exclusion criteria added botanical preparations</li> <li>Prohibited/restricted treatments updated</li> <li>Dose modifications were updated to program standards</li> <li>Immune-mediated adverse events description added</li> <li>RECIST 1.1 updated as per BMS standards</li> </ul>
Amendment 12 (site specific)	01-May-2017	<ul style="list-style-type: none"> <li>Add a China specific sub-study to allow enrollment of patients from China (~130 randomized subjects)</li> </ul>
Revised Protocol 03(incorporates Amendment 11)	31-Aug-2016	<ul style="list-style-type: none"> <li>Extended the time to randomization and modified tissue requirements for eligibility. The period following last dose of chemotherapy has been extended from 7 to 9 weeks (and from 9 to 11 weeks if patients undergo PCI).</li> </ul>

**Table 2.4-1: Protocol Amendments**

Amendments	Date of issue	Summary of Major Changes
		<ul style="list-style-type: none"> <li>• Updates based on nivolumab IB. Changed the requirement to collect amylase and lipase to amylase or lipase. Added amylase or lipase testing to follow up requirements.</li> <li>• [REDACTED]</li> <li>• the timing for PFS analysis was specified to be approximately around 6 months after last patient is randomized,</li> <li>• dose modifications, criteria to resume treatment and discontinuation criteria were and safety algorithms were updated.</li> </ul>
Revised Protocol 02(incorporates Amendment 10)	11-May-2016	<ul style="list-style-type: none"> <li>• Added a bullet to OS language in Section 8.1 and removed - from Section 8.4.5.2.</li> </ul>
Revised Protocol 01 (incorporates Amendment 09 )	20-Apr-2016	<ul style="list-style-type: none"> <li>• [REDACTED]</li> <li>• Clarified acceptable first line radiation treatment for patients with known brain metastasis and timing it must be completed prior to the start of study treatment.</li> <li>• Updated guidance around the use of palliative radiation therapy during study treatment to better support standard practice in the community.</li> <li>• Added guidance for dosing of subjects weighing less than 35kg. Clarified that dosing is not to be skipped in the presence of dose delays but resumed at the next time point.</li> <li>• Clarified guidance for treatment beyond progression. Corrected timing of collection of screening procedures to be within randomization date rather than first treatment date as appropriate.</li> <li>• Provided guidance on the collection of concomitant medications in the follow up setting.</li> <li>• Provided definition of a SUSAR and how they will be reported.</li> <li>• Provided detail on OS data to be provided to DMC</li> </ul>
Original Protocol	07-Jul-2015	<ul style="list-style-type: none"> <li>• Not Applicable</li> </ul>

## 2.5 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) has been established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio. Details of DMC responsibilities and procedures are specified in the DMC charter<sup>3</sup>. Representatives of the Sponsor will serve only as coordinators of the committee, without having full member responsibilities or privileges. In addition, the Sponsor will independently review safety data in a blinded manner during the conduct of this trial to ensure that any safety issues are identified and addressed.

## 2.6 Blinded Independent Central Review (BICR)

A Blinded Independent Central Review (BICR) Committee will review tumor assessments to determine RECIST 1.1 response for the analyses of PFS, ORR and, DOR. PFS (per BICR) and ORR with DOR (per BICR), are secondary and exploratory endpoints for this study respectively. Details of the BICR responsibilities and procedures will be specified in the BICR charter.

## 3 OBJECTIVES

In subjects with ED-SCLC after completion of platinum-based first line chemotherapy:

### 3.1 Primary

- To compare OS of nivolumab in combination with ipilimumab versus placebo in subjects with ED-SCLC after completion of platinum-based first line chemotherapy.

### 3.2 Secondary

- To compare OS of nivolumab versus placebo in subjects with ED-SCLC after completion of platinum-based first line chemotherapy.
- To compare Blinded Independent Central Review (BICR) assessed PFS of nivolumab, and nivolumab in combination with ipilimumab, versus placebo
- To evaluate (descriptively) OS and BICR-assessed PFS of nivolumab combined with ipilimumab versus nivolumab
- To evaluate tumor mutational burden as a predictive biomarker for OS and PFS of nivolumab, and nivolumab in combination with ipilimumab

█ █

█ █

█ █

[REDACTED]

## 4 ENDPOINTS

### 4.1 Primary Endpoint

Overall Survival is defined as the time from randomization to the date of death. A subject who has not died will be censored on the last date the subject was known to be alive.

### 4.2 Secondary Endpoint(s)

Secondary endpoints will be evaluated at the same time as the OS primary endpoint analysis. The OS and PFS secondary endpoints comparing the experimental treatment groups with placebo will be tested hierarchically. The hierarchical order is defined in [section 7.5.3](#).

Secondary endpoint of OS comparing nivolumab monotherapy versus placebo is defined similarly to the primary endpoint.

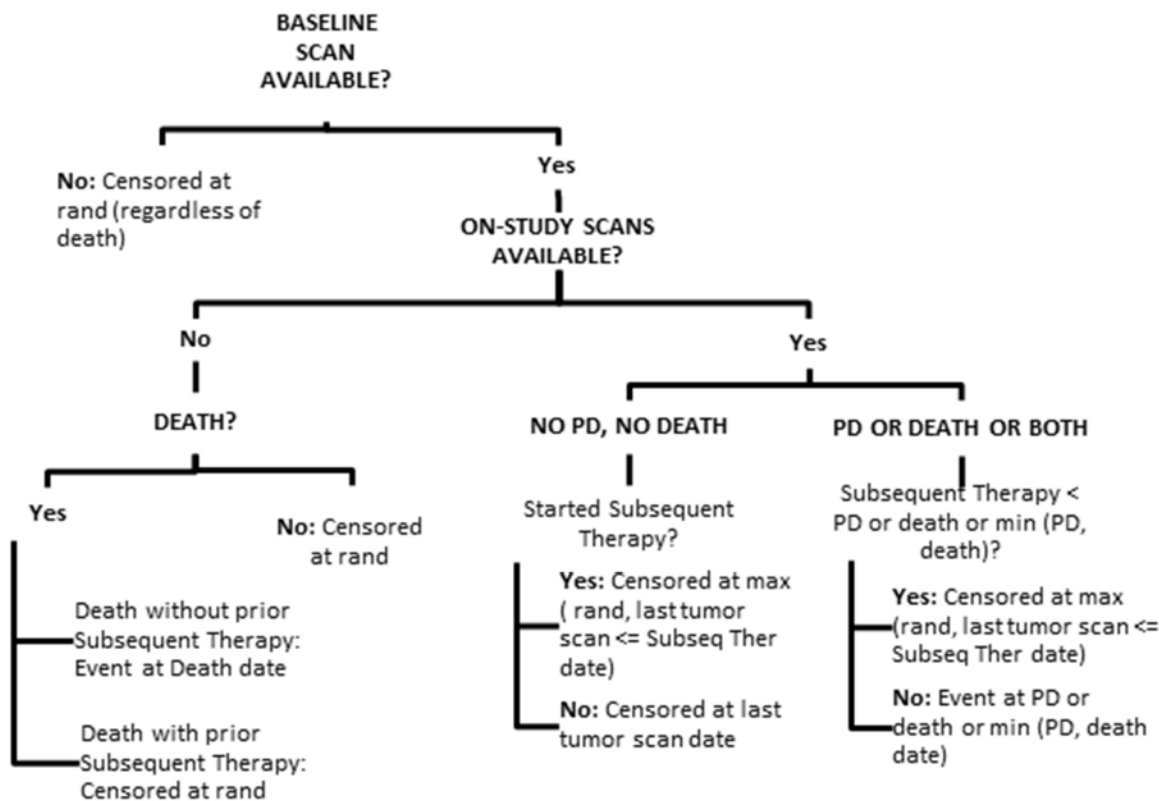
Secondary endpoint PFS will be using PFS as assessed by BICR as primary analysis (sensitivity analysis of PFS will also be conducted using investigator assessment -see [Section 7.5.2.1](#)).

PFS is defined as the time from randomization to the date of first documented progression (per RECIST 1.1) as determined by BICR, or death due to any cause, whichever occurs first. Subjects who die without a reported progression (and die without start of subsequent therapy) will be

considered to have progressed on the date of their death. Subjects who did not have documented PD per BICR per RECIST1.1 criteria and who did not die will be censored on the date of their last evaluable tumor assessment on or prior to initiation of the subsequent anti-cancer therapy. Subjects who did not have any on study tumor assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) will be censored on the randomization date. Subjects who started any subsequent anti-cancer therapy without a prior reported PD per BICR will be censored at the last evaluable tumor assessment on or prior to initiation of the subsequent anti-cancer therapy.

See Figure 4.2-1 for the graphical representation of this definition.

**Figure 4.2-1: Graphic Display of PFS Definition**



rand = randomization, STh = Subsequent Therapy

An OS descriptive analysis will be performed to evaluate nivolumab monotherapy versus nivolumab with ipilimumab treatment regimen. OS definition is similar to the primary endpoint.

Tumor Mutation Burden (TMB) is measured using FoundationOne CDx™ (F1CDx) assay, a comprehensive genomic profile (CGP) assay based on baseline tumor tissue. TMB is defined as



the number of somatic, coding, base substitution, and indel mutations per megabase of genome examined.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



#### **4.3.4 Safety Endpoints**

Safety and tolerability will be measured by the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose delay, select adverse events and specific laboratory abnormalities (worst grade) 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 SAP<sup>4</sup>

#### **4.3.5 Pharmacokinetics**

Pharmacokinetic serum samples will be collected to characterize pharmacokinetics of nivolumab and to explore exposure-safety and exposure-efficacy relationships.

#### **4.3.6 Immunogenicity**

Blood samples for immunogenicity analysis will be collected from subjects assigned to the experimental treatment group(s) according to the protocol schedule. Samples will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemiluminescent (ECL) immunoassay.

#### **4.3.7 Outcomes Research**

Patients' overall health status will be assessed using the The EuroQol Group's self-reported health status measure (EQ-5D)<sup>5</sup>. EQ-5D essentially has 2 components- the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises

the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state)<sup>6</sup>.

## 5 SAMPLE SIZE AND POWER

Per original protocol, approximately 810 subjects were to be randomized to three treatment arms in a 1:1:1 ratio.

The primary objective is to compare OS of nivolumab in combination with ipilimumab versus placebo. The analysis of primary endpoint of OS will be conducted when at least 386 deaths have been observed pooled across the two treatment groups. With 386 events available for comparison of OS in nivolumab in combination with ipilimumab vs placebo, power of the log-rank test is approximately 90% to detect a hazard ratio (HR) of 0.72 with a type I error of 0.05 (two-sided). The critical hazard ratio for determining whether nivolumab in combination with ipilimumab is superior to placebo is 0.82.

Power calculations were performed using EAST® Software (version 6.4.1). Results were generated by 10000 simulations. Model assumptions were as follows:

Survival function for placebo arm was modeled using a four hazard pieces: OS rates at 3, 9, 18 and 26 months were assumed to be 90%, 47%, 15% and 9%, respectively, based on published survival curve for placebo maintenance in extensive-stage disease SCLC, adjusted for induction phase<sup>7</sup>.

For nivolumab in combination with ipilimumab, a delayed effect versus placebo with a hazard ratio (HR) of 1 for the first 3 months<sup>8</sup> and an HR of 0.68 thereafter was assumed, resulting into overall HR (experim over placebo) of 0.72 at time of the OS analysis, as determined from the 10000 simulations.

Median OS derived from the survival functions were 8.8 months and 11.0 months for the placebo and experimental treatment groups, respectively. Accrual information used in the simulations had the same pattern as the actual data at time of the protocol amendment (832 subjects were accrued in 28 months and randomized to the three treatment groups). A 5% probability of dropout by month 6 was taken into account. Given the observed accrual and dropout and survival assumptions it is expected that the duration of the study from start of randomization to analysis of OS will be approximately 35 months (28 months of accrual + 7 months of follow-up, providing an average follow up of 9 months).

The secondary endpoints of OS in nivolumab vs placebo and PFS in experimental treatments vs placebo will be tested hierarchically (see [Section 7.5.3](#)). Assuming 386 events are also available for comparison of OS in nivolumab vs placebo, power of the log-rank test is approximately 90% to detect a hazard ratio (HR) of 0.72 with a type I error of 0.05 (two-sided).

For PFS analyses comparing nivolumab or nivolumab in combination with ipilimumab vs placebo in all randomized subjects, 525 PFS events are projected to be observed at the time of

the OS analysis, which provides approximately 93% power to the log-rank test to detect an overall HR of 0.74 with a Type I error of 0.05 (two-sided). Piecewise exponential distributions were used to model PFS. The following assumptions were made: for the placebo group, a median PFS of 2 months and PFS rate at 12 months of 5% were assumed<sup>8,9,10</sup>. Both experimental arms were assumed to have median PFS of 2 months (similar to placebo), with PFS rate at 12 months of 15%<sup>2</sup>.

This study includes a sub-study to allow enrollment of patients from China (site-specific protocol Amendment 12). Data from these additional subjects will be reported separately. Subjects from China randomized on or before end of global study accrual will be included in the population used for the primary analysis clinical study report. The required number of deaths for the primary OS analysis is based on the global study population.

## 6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

### 6.1 Study Periods

See Core Safety SAP<sup>4</sup>.

### 6.2 Treatment Regimens

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

- Arm A: Experimental Arm (monotherapy) nivolumab
- Arm B: Experimental Arm (combination) nivolumab + ipilimumab
- Arm C: Placebo Arm (placebo for both nivolumab and ipilimumab)

The treatment group “**as treated**” will be the same as the arm randomized by IVRS. However, if a subject received the incorrect drug for **the entire period** of treatment, the subject’s treatment group will be defined as the incorrect drug the subject actually received.

### 6.3 Populations for Analyses

- **Global study population:** all subjects enrolled during the global accrual window (from first patient first consent date to last patient outside of China’s consent date). Any patient from China enrolled during the global accrual window will be included.
- **All Enrolled Subjects:** All subjects who signed an informed consent form and are registered into IVRS during the global enrollment period
- **All Randomized Subjects:** All enrolled subjects from global study population who were randomized to any treatment group.
- **All Treated Subjects:** All randomized subjects from global study population who received at least one dose of any study medication.

- All Randomized subjects with at least one lesion at baseline : All randomized subjects from global study population with at least one lesion (target or non target) at baseline scan
- **PK Subjects:** All randomized subjects from global study population with available serum time-concentration data.
- **Immunogenicity Subjects:** All randomized subjects from global study population with available Anti Drug Antibody data.
- **Tumor Mutation Burden (TMB) evaluable Subjects:** All randomized subjects from global study population with baseline evaluable TMB.
- **China Cohort:** Subjects enrolled from China Mainland

## 7 STATISTICAL ANALYSES

Primary population of analysis is the global study population. Demography, baseline characteristics, efficacy and safety will also be reported for the China cohort separately, analyses will be descriptive.

### 7.1 General Methods

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

Time to event distribution (i.e. progression free survival, overall survival and duration of response) will be estimated using Kaplan Meier techniques.

Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survivor function  $S(t)$ <sup>11,12</sup>. Rates at fixed timepoints (e.g. OS at 6 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula<sup>13</sup> for variance derivation and on log-log transformation applied on the survivor function  $S(t)$ <sup>14</sup>.

Unless otherwise specified, the stratified log-rank test will be performed to test the comparison between time to event distributions (OS and PFS). Stratification factors will be ECOG PS (0, 1), sex (male, female) and Prophylactic Cranial Irradiation (PCI) following chemotherapy (yes, no), as entered into the IVRS.

Unless otherwise specified, the stratified hazard ratio between 2 treatment groups along with CI will be obtained by fitting a stratified Cox model with the treatment group variable as unique covariate. Stratification factors will be same as above.

Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method<sup>15</sup>. The difference in rates between the two treatment arms along with their two-sided

95% CI will be estimated using the following Cochran-Mantel-Haenszel (CMH) method of weighting<sup>16</sup>, adjusting for the stratification factors:

$$\hat{\theta} = \frac{\sum_i w_i \hat{\theta}_i}{\sum_i w_i} \sim N \left[ \theta, \frac{\sum_i w_i^2 \left[ \frac{p_{ix}(1-p_{ix})}{n_{ix}-1} + \frac{p_{iy}(1-p_{iy})}{n_{iy}-1} \right]}{\left( \sum_i w_i \right)^2} \right]$$

where  $\hat{\theta} = p_{ix} - p_{iy}$  is the rate difference of the *i*th stratum,  $w_i = \frac{n_{ix}n_{iy}}{n_{ix} + n_{iy}}$ , and  $n_{ix}$  and  $n_{iy}$  are the number of subjects randomized to treatments x and y, respectively, in the *i*th stratum.

Stratification factors will be the same as above. Associated odds-ratio will be derived.

The p-values from sensitivity analyses for efficacy endpoints are for descriptive purpose only and not adjusted for multiplicity.

## 7.2 Study Conduct

### 7.2.1 Accrual

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

### 7.2.2 Relevant Protocol Deviation

The relevant protocol deviations will be summarized for all randomized subjects, by treatment group and overall. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations. 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.

#### Eligibility:

- Subjects with wrong cancer diagnosis :subjects with cell type other than small cell carcinoma
- Subject with baseline ECOG PS > 1.
- Subjects who received prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)
- Subjects who received prior treatment other than acceptable combinations, as recommended per NCCN guidelines, include cisplatin or carboplatin combined with either etoposide or irinotecan.

- Subjects who received more than 4 cycles of platinum Chemo
- Subjects with best response to first line chemotherapy not CR, PR, or SD or progressed before randomization
- Subjects who received less than 4 cycles of platinum-based first line chemotherapy and reason regimen was discontinued not due to toxicity

#### On-Study:

- Subjects receiving concurrent anti-cancer therapy (defined as chemotherapy, hormonal therapy, immunotherapy, radiation therapy other than those allowed per protocol- i.e. Palliative bone radiotherapy, or palliative radiotherapy to a single metastatic site, other than bone, standard or investigational agents for treatment of SCLC).
- Subject treated differently as randomized (subjects who received the wrong treatment, excluding the never treated).

A subject listing will also be produced.

### **7.2.3 Unblinding**

A summary of subjects whose treatment was unblinded during the course of the study and reason for being unblinded will be provided based on a cumulative unblinding report prepared by a randomization coordinator within BMS.

## **7.3 Study Population**

Unless otherwise specified, analyses will be performed on the all randomized population.

### **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.

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

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment group as treated.

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

### **7.3.2 Demographics and Other Baseline Characteristics**

Descriptive statistics will be summarized for the following baseline characteristics by treatment group as randomized, for the global population and for the subset of subjects with high TMB.

- Age (descriptive statistics)
- Age category (< 65, ≥ 65 and < 75, ≥ 75 and < 85, ≥ 85; ≥ 75, ≥ 65)
- Sex (male/female) (CRF source)
- Race (White/ Black or African American /Asian/Other)
- Region (US/Canada vs. Asia vs. Europe vs. ROW)
- Baseline ECOG Performance Status (0/1) (CRF source)
- Baseline LDH (≤ ULN, > ULN)
- Baseline weight (descriptive statistics)
- Time from Initial Disease Diagnosis to Randomization (<6mo, 6mo- 1 year, 1 - < 2 year, ≥ 2 year)
- Baseline metastasis (Yes/No): CNS, Liver, both
- Sites of diseases (all lesions) per investigator
- Tumor burden: sum of the diameters of target lesions at baseline
- Smoking status (current/former, never smoker, unknown)
  
- Similarly the following IVRS data will be summarized by treatment group as randomized.
- ECOG Performance Status: 0 vs. 1
- Sex: Male vs. Female
- Prophylactic Cranial Irradiation (PCI) following chemotherapy: Yes vs. No

### **7.3.3 Medical History**

General medical history will be listed by subject and pretreatment events will be tabulated.

### **7.3.4 Prior Anti-Cancer Therapy**

Prior anti-cancer therapy will be summarized. Following information will be presented

- Received prior systemic cancer therapy (Yes/no)
  - 1st Line Therapy
    - ◆ Agents (carboplatin, cisplatin, etoposide, irinotecan, ...)
    - ◆ Number of cycles received
    - ◆ Best response to 1<sup>st</sup> Line
    - ◆ Primary reason for discontinuation
    - ◆ Median time from last dose of first line chemotherapy to randomization (also split by category < 4 weeks, 4 - 6 weeks, > 6 - 9 weeks, > 9 weeks)



- Received prior radiotherapy (yes or no).
  - type of RT (Prophylactic Cranial Irradiation (PCI), whole brain radiation therapy, other)
  - Time from last RT to randomization (Subjects receiving PCI or Brain RT) (< 3 weeks, 3 - 11 weeks, > 11 weeks )
- Received prior surgery related to current cancer (yes or no)
- Other Prior therapy:
- Prior/current non-study medication classified by anatomic and therapeutic classes.

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 examination will be tabulated by examination criteria and by treatment group.

### **7.3.6 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**

Unless otherwise specified, analyses in this section will be performed using all treated subjects, by treatment group as treated.

### **7.4.1 Administration of Study Therapy**

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

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

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

- Number of doses received (nivolumab and ipilimumab)

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%;  $\geq$  110%. (nivolumab and ipilimumab)

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.

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.

- Below table summarizes the key parameters used to calculate dosing data.





## **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 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.

## **7.4.3 Concomitant Medications**

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

The following summary table will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term)

A by-subject listing will accompany the table.

## 7.5 Efficacy

### 7.5.1 Overall Survival Analysis

OS for each of the two experimental arms will be compared to the control group using a two-sided log-rank test stratified by ECOG Performance Status (0 vs. 1), Gender (male vs female) and Prophylactic Cranial Irradiation (PCI) following chemotherapy (Yes vs. No) (IVRS source) in all randomized subjects. Hierarchical test procedure will be used to control the overall Type I error rate at 0.05 (see [Section 7.5.3](#)).

HRs and corresponding two-sided CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. Additionally, a descriptive HR and corresponding two-sided 95% CI will be provided to evaluate differences between the two experimental arms.

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.

Survival rates at 6, 9, 12, and 18 months will be estimated using KM estimates on the OS curve for each treatment group. Minimum follow-up must be longer than the timepoint to generate the rate. Associated two-sided 95% CIs will be calculated.

The status of subjects who are censored in the OS KM analysis (all randomized subjects) 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.)

To examine the assumption of proportional hazards in the Cox regression model, in addition to treatment, a time-dependent variable defined by treatment by time interaction will be added into the model. A two-sided Wald Chi-square p-value of less than 0.1 may indicate a potential non-constant treatment effect.

#### 7.5.1.1 OS Sensitivity Analysis

The following OS sensitivity analyses will be conducted using all randomized subjects. Estimates of the HRs and corresponding two-sided CIs will be provided using stratified (unless otherwise noted) Cox proportional hazards model, with treatment group as a single covariate.

- OS for each of the two experimental arms will be compared to the control group using a two-sided unstratified log-rank test.
- OS will be compared between treatment groups *using the strata as determined at baseline* (CRF source). This analysis will be performed only if at least one stratification variable at IVRS and at baseline disagrees for at least 10% of the randomized subjects.

### **7.5.1.2 OS Subgroup Analysis**

OS subgroup analysis will be conducted using all randomized subjects. To assess consistency of treatment effects (nivo plus ipi vs. placebo and nivo monotherapy vs. placebo) in different subsets, a “forest” plot of the OS unstratified hazard ratios (and 95% CIs) will be produced for the following variables:

- Baseline ECOG Performance Status (0 vs. 1) (CRF source)
- Sex (male vs female) (CRF source)
- Prophylactic Cranial Irradiation (PCI) following chemotherapy (Yes vs No) (CRF source)
- Race (Asian; Black/African American; White; American Indian/Alaska Native; Native Hawaiian/Other Pacific Islander, Other)
- Ethnicity
- Age categorization
  - < 65,
  - ≥ 65 and < 75
  - ≥ 75 and < 85
  - ≥ 85
  - ≥ 75
  - ≥ 65
- Region (US/Canada vs. Asia vs. Europe vs. ROW)
- Baseline CNS metastases (yes/no)
- Baseline Liver metastases (yes/no)
- Baseline LDH ( $\leq$  ULN vs.  $>$  ULN)
- Best response to 1<sup>st</sup> line (CR/PR vs. SD vs. other).
- Time from last dose of 1st line chemotherapy to randomization (<4, 4-6, 6-9, >9 weeks)

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

### **7.5.1.3 OS Multivariate Analysis**

A multivariate Cox model will be fitted to assess the treatment effect on OS when adjusted for potential prognostic factors. The following prognostic factors will be included in the model.

- ECOG Performance Status (0 vs. 1) (CRF source)
- Sex (male vs. female) (CRF source)
- Prophylactic Cranial Irradiation (PCI) following chemotherapy (Yes vs. No) (CRF source)
- Age category (< 65 - ≥ 65).
- Presence of Liver Metastasis at baseline (Y/N)
- Baseline LDH ( $>$  ULN vs. other)

- Best response to 1st line (CR/PR vs. other)

Analysis assessing adjusted treatment effect of ipi +nivo combo vs placebo and nivo monotherapy vs placebo will be conducted. HRs and corresponding 95% CIs will be provided for treatment variable and all covariates.

#### **7.5.1.4 OS from Start of Prior Systemic Cancer Therapy**

Overall Survival from start of prior systemic cancer therapy OS curves will be estimated, for each treatment group, using the Kaplan-Meier (KM) product-limit method. Median OS and corresponding two-sided, 95% confidence intervals will be computed.

#### **7.5.2 BICR Progression Free Survival**

BICR-assessed PFS for each of the two experimental arms will be compared to the control group using a two-sided log-rank test stratified by the same stratification factors as in the OS primary analysis. The secondary PFS endpoints will be tested hierarchically (see [Section 7.5.3](#)). If superiority of OS of nivolumab monotherapy over placebo comparison is not demonstrated, PFS is not tested

HRs and corresponding two-sided CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the same stratification factors as in the OS primary analysis. Descriptive HR and corresponding two-sided 95% CI will be provided to evaluate differences between the two experimental arms.

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

PFS rates at 6, 9, 12, and 18 months will be estimated using KM estimates on the PFS curve for each treatment group. Minimum follow-up must be longer than the timepoint to generate the rate. Associated two-sided 95% CIs will be calculated.

The source of progression event (death versus progression) will be summarized by treatment group. The status of subjects who are censored in the PFS analysis will be tabulated for each treatment group using the following categories. This summary will be provided for all randomized subjects.

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



### 7.5.2.1 PFS Sensitivity Analysis

Sensitivity analyses of PFS will be performed using the following modification of PFS primary definition. Estimate of HR, two sided 95% CI and p-value will be presented

- PFS will be compared between treatment groups *using the strata as determined at baseline* (CRF source). This analysis will be performed only if at least one stratification variable at IVRS and at baseline disagrees for at least 10% of the randomized subjects.
- *PFS accounting for assessment after subsequent therapy* subjects will be defined similarly to the primary definition except that events (progression or death) and tumor assessments that occurred on or after subsequent anticancer therapy will be taken into account (see Table 7.5.2.1-1).
- *PFS accounting for missing tumor assessment prior to PFS event (progression or death)*. This analysis will be performed only if at least 20% of events have missing prior tumor assessment. It will apply the following restriction to the primary definition: If the elapsed time between the PFS event and the last on-study assessment immediately prior to the event (or randomization date if no on-study scan) is two or more missed visits (more than 12 weeks + 10 days), the subject will be censored at his last tumor assessment prior to the PFS event, or randomization date if no on-study scan.
- *PFS accounting for assessment after palliative radiotherapy received as subsequent anti-cancer therapy*. This analysis is similar to the primary analysis except that no censoring will occur for palliative radiotherapy after first dose of treatment.

PFS will also be analyzed per investigator assessment. PFS KM curves for each treatment group will be generated. Stratified hazard ratio and corresponding two-sided 95% CI, median PFS and corresponding two-sided, 95% CI will be presented

**Table 7.5.2.1-1: Censoring Scheme 1 for Sensitivity Analysis of PFS**

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression	Date of first documented progression per RECIST 1.1 (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
Death without progression	Date of death	Progressed

### **7.5.2.2 PFS Subgroup Analysis**

PFS subgroup analysis will be performed using all randomized subjects. To assess consistency of treatment effect in PFS in different subgroups, a ‘forest’ plot of the PFS unstratified hazard ratios (comparing nivo + ipi combo vs. placebo and nivo monotherapy vs. placebo) and two-sided 95% CIs will be produced for the same variables as for the OS subgroup analysis. If a subgroup category has less than 10 subjects per treatment group, HR will not be computed/displayed.

### **7.5.2.3 PFS Multivariate Analysis**

The following PFS multivariate analysis will be performed using all randomized subjects

A multivariate Cox model will be fitted to assess the treatment effect on PFS when adjusted for potential prognostic factors. The following prognostic factors will be included in the model.

- ECOG Performance Status (0 vs. 1) (CRF source)
- Sex (male vs female) (CRF source)
- Prophylactic Cranial Irradiation (PCI) following chemotherapy (Yes vs. No) (CRF source)
- Age category (< 65 - ≥ 65).
- Presence of Liver Metastasis at baseline (Y/N)
- Baseline LDH (≤ ULN vs. > ULN)
- best response to 1st line (CR/PR vs. other)

Analysis assessing adjusted treatment effect of ipi + nivo combo vs. placebo and nivo monotherapy vs. placebo will be performed. HRs and corresponding 95% CIs will be provided for treatment variable and all covariates.

### **7.5.3 Protection of Type I Error Across Primary and Secondary Endpoints**

An overall hierarchical testing procedure<sup>17</sup> will be used to assess the secondary endpoints. OS comparing nivolumab monotherapy vs placebo will be tested using 2-sided 5% alpha, if superiority of nivolumab in combination with ipilimumab over placebo is demonstrated at the 5% significance level.

Additionally, if superiority in OS of nivolumab monotherapy over placebo is demonstrated, the 5% alpha will be passed to test the secondary endpoints of PFS. PFS will be tested hierarchically, starting with the comparison of PFS of nivolumab plus ipilimumab with placebo, followed by, if superiority in PFS of nivolumab combined with ipilimumab over placebo is demonstrated, comparison of PFS of nivolumab monotherapy with placebo.



[REDACTED]

## Other Analyses

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

- 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, a waterfall plot showing the best reduction in target lesion tumor burden based on investigator assessment.

### **7.5.5 Extent and Currentness of Follow-Up**

The extent of follow-up for OS 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 randomized subjects.

The currentness of follow-up for OS, defined as the time between last OS contact (i.e., 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, > 0 - 3, > 3 - 6, > 6 - 9, > 9 - 12, and 12 or more months.

Similarly, currentness of PFS follow-up defined as the time from last tumor assessment to data cut-off in months will be summarized by treatment group. Subjects who have a PFS event will be considered as current.

### **7.6 Subsequent Therapy**

Number and percentage of subjects receiving subsequent therapies including radiotherapies, surgeries and systemic therapies will be reported for all randomized subjects.

- Subsequent Therapy
  - Chemotherapy by drug name
  - Immunotherapy (anti-PD1/L1 agents, anti-CTLA4 agents and others, by drug name)
  - Targeted therapy by drug name
  - Other investigational agents by drug name
  - Surgery
  - Radiotherapy
  - Any combination of the above
- By Subject Listing of Subsequent Therapy

### **7.7 Interim Analysis**

Not applicable.

## **7.8 Safety**

### **7.8.1 Deaths**

See core Safety SAP<sup>4</sup>.

### **7.8.2 Serious Adverse Events**

See core Safety SAP<sup>4</sup>.

### **7.8.3 Adverse Events Leading to Discontinuation of Study Therapy**

See core Safety SAP<sup>4</sup>.

### **7.8.4 Adverse Events Leading to Dose Modification**

See core Safety SAP<sup>4</sup>.

### **7.8.5 Adverse Events**

See core Safety SAP<sup>4</sup>.

### **7.8.6 Multiple Events**

See core Safety SAP<sup>4</sup>.

### **7.8.7 Select Adverse Events**

See core Safety SAP<sup>4</sup>.

### **7.8.8 Immune Mediated Adverse Events**

See core Safety SAP<sup>4</sup>.

### **7.8.9 Clinical Laboratory Evaluations**

#### **7.8.9.1 Hematology**

See core Safety SAP<sup>4</sup>.

### **7.8.9.2 Serum Chemistry**

Amylase and lipase will be summarized in addition to the serum chemistry parameters described in the See core Safety SAP<sup>4</sup>.

### **7.8.10 Vital Signs and Pulse Oximetry**

See core Safety SAP<sup>4</sup>.

### **7.8.11 Immunogenicity Analysis**

See core Safety SAP<sup>4</sup>

### **7.8.12 Pregnancy**

By-subject listing of pregnancy tests results will be provided

### **7.8.13 Clinical Safety Program (CSP)**

See core Safety SAP<sup>4</sup>.

## **7.9 Pharmacokinetics**

The 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 to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). Model determined exposures will be used for exposure-response analyses of selected efficacy and safety end points. Results of population PK and exposure-response analyses will be reported separately.

[REDACTED]

### **7.10.1 Tumor Mutation Burden**

#### **7.10.1.1 Descriptive analysis of TMB distribution**

- Tumor specimen characteristics will be summarized by treatment group using all randomized subjects.

- Summary of TMB distribution using descriptive statistics, proportion of subjects with high/low TMB using pre-defined cutoff values at 10, 11, 13, 14 and 15 mutations/MB will be presented by treatment group and overall using all TMB-evaluable subjects.
- Cumulative distribution of TMB will be displayed by treatment group and overall using all TMB-evaluable subjects.
- Listing of all TMB data will be provided for all randomized subjects.

### **7.10.1.2 Demography/Baseline Characteristics/Efficacy of the TMB-evaluable population**

Due to the evolving nature of the TMB investigation, there will be some subjects for which there are not adequate samples for evaluation of TMB. In addition, the TMB evaluation process has an inherent test failure rate, even with adequate sample available. Given these considerations, it will be necessary to evaluate whether results in the TMB-evaluable population are in general concordance with the ITT population.

To evaluate whether results in the TMB-evaluable population are in general concordance with all randomized population, the following analyses will be performed:

- Descriptive statistics for demographic and other baseline characteristics as described in [Section 7.3](#), will be summarized by treatment group as randomized, using TMB evaluable population
- The following efficacy endpoints analyses will be conducted by tumor mutational burden availability at baseline, using all randomized population: OS/PFS per BICR (summary tables and KM plots), ORR and DOR per BICR (summary tables). Analyses will be similar as done for all randomized but analyses will descriptive only (no testing).
- The information pertaining to subsequent therapies as described in [Section 7.9](#) will be summarized for the TMB evaluable population by treatment group

### **7.10.1.3 Association between TMB and Efficacy, TMB-evaluable subjects**

The following exploratory analyses of efficacy endpoints will be provided for TMB-evaluable subjects. Treatment effects that will be assessed will be nivo + ipi vs. placebo and nivo vs. placebo. Unless otherwise noted, cutoffs at 10, 11, 13, 14 and 15 mutations/MB will be explored. At each cutoff, TMB Subgroups are defined as follows: TMB high: subjects with TMB  $\geq$  cutoff values, TMB low subjects with TMB  $<$  cutoff value

#### **OS/PFS by TMB**

A summary of OS by TMB status (high vs. low) will be presented by treatment group. OS function for each TMB subgroup will be estimated using the KM product limit method for each treatment arm and will be displayed graphically. A two-sided 95% CI for median OS in each arm will be computed via the log-log transformation method. Hazard ratios of OS and corresponding

two-sided 95% CI will be estimated using an unstratified Cox proportional hazard model, with treatment group as a single covariate.

OS HR comparing TMB high vs. TMB low subgroups among TMB-evaluable subjects from nivo + ipi arm will be displayed graphically as a function of TMB cutpoint. Cutoffs at 6, 8, 9, 10, 11, 13, 14, and 15 will be analyzed to visualize which TMB cutpoint gives the maximum difference between TMB high vs. low subgroups. Nivo mono arm will be analyzed similarly. Same plot will be generated for subjects randomized to placebo, to visualize potential prognostic effect of TMB on OS.

A Cox proportional hazards regression model will be fitted for OS with treatment (nivo + ipi vs. placebo), TMB status (high vs. low), and treatment by TMB status interaction. Although the study is not designed to have appropriate power to formally test the interaction of the model, an interaction test at significance level of 0.2 will warrant further exploration and the following statistics will be reported: interaction p-value, HR of Nivo + ipi vs. placebo and its associated 95% CI for each TMB subgroup, HR of TMB high vs. TMB low and its associated 95% CI for each treatment group. Idem for Nivo mono vs. placebo comparison.

Similar analysis will be run on PFS (per BICR assessment).



## 7.11 Outcomes Research Analyses

The outcome research analyses will be performed using all randomized subjects.

### 7.11.1 LCSS questionnaire

LCSS questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (i.e., the number of subjects still on treatment or in follow-up), will be calculated and summarized at each assessment point.



Baseline and change from baseline of the average symptom burden index score at each assessment point will be summarized using descriptive statistics (N, mean, median, SD, 25<sup>th</sup> and 75<sup>th</sup> percentiles) by treatment group, as randomized.

Kaplan-Meier plots for TTSD as measured by LCSS ASBI will be presented along with median TTSD and corresponding 95% CI. Hazard ratios and corresponding two-sided 95% CI will be estimated using unstratified Cox proportional hazard model, with treatment group as a single covariate. TTSD rates at fixed timepoints Week 6, 12 and 24 will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula<sup>13</sup> for variance derivation and on log-log transformation applied on the survivor function  $S(t)$ <sup>18</sup>.

### **7.11.2 EQ-5D questionnaire**

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized along with change from baseline using descriptive statistics (N, mean, SD, median, 25<sup>th</sup> and 75<sup>th</sup> percentiles) by treatment group, as randomized.

Subject's overall health state on EQ-5D index using UK weighting algorithm at each assessment time point will be summarized along with change from baseline using descriptive statistics (N, mean, SD, median, 25<sup>th</sup> and 75<sup>th</sup> percentiles) by treatment group, as randomized.

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, as randomized. Percentages will be based on number subjects assessed at assessment time point.

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**

The following convention will be used for BIRC data:

BICR data will consist of two sets of results from two different reads (i.e. Reader 1 and Reader 2). If adjudication occurred, results from reader with whom the adjudicator agrees will be used for analysis. If adjudication did not occur, results from Reader 1 will be used for analysis.

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<sup>19</sup>.

- Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in Section 4.3.3 of BMS Non-Study Medication Domain Requirements Specification<sup>20</sup>.

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 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.
- For other partial/missing dates, the following conventions may be used:
- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, “July 1” will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

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

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

$$\text{Duration} = (\text{Last date} - \text{first date} + 1)$$

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.

## APPENDIX 1 DOCUMENT HISTORY

Version Number	Date	Author(s)	Description
1.0		Christine Baudelet	
2.0	27Sep2018	Christine Baudelet	<p>SAP revised to align with revised CA209451 protocol v06</p> <ul style="list-style-type: none"> <li>-Moved OS of nivolumab vs placebo to secondary objectives</li> <li>-Section 5: Sample size and power: updated sample size and power analysis</li> <li>-Section 7.5.3: Hierarchical test procedure is used to control the type I error at 5% across primary and secondary OS/PFS endpoints</li> <li>-Section 4.3.1 Objective response rate: Population for analysis of objective response rate (ORR) changed to all randomized subjects with at least one lesion at baseline. Population defined in section 6.3</li> </ul> <p>Other changes:</p> <ul style="list-style-type: none"> <li>-Section 7.3.4 Prior anti-cancer therapy: revised categories for time from last dose of first line chemotherapy to randomization</li> <li>-Section 7.5 Efficacy analysis by subgroup : Time from last dose of 1st line chemotherapy to randomization (&lt;4, 4-6, 6-9, &gt;9 weeks) added</li> <li>-Section 4.3.3 Time to Symptom deterioration(TTSD): rule about using common time point removed as same assessment schedules for all arms</li> <li>-Section 7.11 Outcomes research analyses: HR estimates of time to symptom deterioration added.</li> </ul>



