Official Title of Study:

A PHASE 1/2, OPEN-LABEL STUDY OF NIVOLUMAB MONOTHERAPY OR NIVOLUMAB COMBINED WITH IPILIMUMAB IN SUBJECTS WITH ADVANCED OR METASTATIC SOLID TUMORS

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STATISTICAL ANALYSIS PLAN
FOR CINICAL STUDY REPORT

A PHASE 1/2, OPEN-LABEL STUDY OF NIVOLUMAB MONOTHERAPY OR NIVOLUMAB COMBINED WITH IPILIMUMAB IN SUBJECTS WITH ADVANCED OR METASTATIC SOLID TUMORS

PROTOCOL CA209032

VERSION # 2.0

TABLE 1: REVISION HISTORY

Revision	Date	Revised By	Changes Made -- Reasons for the Change
1.0	07 OCT 2013		Original issue
2.0	26 FEB 2016	[redacted]	Incorporates Amendments 08, 09, and 10. Summary of changes: **Amendment 08** is to add nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg to the dose levels being investigated in study CA209-032, change the bladder cohort to a One Stage Design. **Amendment 09 includes:** • SCLC and Bladder: arms Nivo 3 mg/kg and Nivo 1/ Ipi 3 mg/kg, increase sample size. • Updates to Blinded Independent Central Review (BICR) information • Updates to Primary, Secondary [redacted] Objectives **Amendment 10 includes:** • Regimen NI2c was added for treatment of ovarian cancer. • For subjects from NI combination who undergo a re-exposure if they achieved an initial objective response (PR or CR) or stable disease of > 3 months and had a subsequent documented progression, an option to continue treatment with nivolumab monotherapy if ipilimumab treatment was stopped due to toxicity is added. (see Section 2.4 for details)

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2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 1/2, open-label study of nivolumab monotherapy (Arm N), or nivolumab combined with ipilimumab (Arm N-I) in adult (≥ 18 years) subjects with advanced or metastatic cancer of the following types:

1) Triple Negative Breast Cancer (TNBC)
2) Gastric or Gastro-Esophageal Junction Carcinoma (GC)
3) Pancreatic Cancer (PC)
4) Small Cell Lung Cancer (SCLC)
5) Bladder Cancer (BC).
6) Ovarian Cancer (OC)

The assignment to treatment arm and evaluation of safety and activity will be performed independently for each tumor type. For each tumor type, subjects will be assigned to one of these treatment arms:

Arm N: Nivolumab monotherapy (3 mg/kg) Q2W

Arm N-I Dose Level 1: Nivolumab (1 mk/kg) + Ipilimumab (1 mg/kg) Q3W for 4 doses, then Nivolumab (3 mg/kg) Q2W

Arm N-I Dose Level 2: Nivolumab (1 mk/kg) + Ipilimumab (3 mg/kg) Q3W for 4 doses, then Nivolumab (3 mg/kg) Q2W

Arm N-I Dose Level 2b: Nivolumab (3 mk/kg) + Ipilimumab (1 mg/kg) Q3W for 4 doses, then Nivolumab (3 mg/kg) Q2W

Arm N-I Dose Level 2c: Nivolumab (3 mk/kg) Q2W + Ipilimumab (1 mg/kg) Q6W

Additional cancer types may also be added in the future. The addition of any new cancer types will not affect the statistical analysis plan. All analyses related to the additional cancer types will be performed exactly as described in this SAP.

Dose-Escalation Safety Evaluation Phase for Combination Arm: Although the regimen currently used in the phase 3 melanoma study, nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg, was expected to also be tolerable in the tumors studied here, an initial dose-escalating safety evaluation for the combination arms was conducted for each subject with GC, PC, TNBC, or SCLC. The BC cohort was added to this protocol following the completion of the safety evaluations in GC, PC, TNBC, and SCLC at dose level 1 (nivolumab 1 mg/kg, ipilimumab 1 mg/kg) which did not reveal safety concerns. Thereby the starting dose level for the BC cohort was dose level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg). Six BC patients were initially randomized to Dose Level 2, after which enrollment to Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg) began.

Enrollment to Stage 1 for Arm N will occur in parallel to the safety evaluation for Arm N-I.

Modified Design for Bladder Cancer Cohort:

Bladder arms N and N-I (Dose Levels 2 and 2b) will be conducted as a One Stage Design with the treatment of 26-105 subjects in each arm. The Safety Evaluation Phase for the N-I arm will start at Dose Level 2 (nivolumab 1 mg/kg, ipilimumab 3 mg/kg) and will evaluate safety and tolerability after the first 6 randomized subjects. Following the N-I safety evaluation phase, Dose Levels 2 will enroll 26 subjects and 2b will enroll up to a total of 105 subjects. Based on the safety evaluations thus far on study, no dose escalation phase is necessary for bladder cohort N-I Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg).

Modified Design for Ovarian Cancer Cohort:

Ovarian arm N-I (Dose Levels 2, 2b and 2c) will be conducted as a One Stage Design with the treatment of 40 subjects in each arm. Based on the safety evaluations thus far on study, no dose escalation phase is necessary for ovarian cohort N-I Dose Levels.

SCLC Expansion:

SCLC cohorts Arm N and Arm N-I met the pre-specified safety and efficacy criteria and proceeded to Stage 2. Based on an interim data review, disease control rates (SD + PR + CR) of 36% and 57% for Arms N and N-I, respectively, were estimated. In order to further investigate nivolumab and nivolumab combined with ipilimumab activity in specific SCLC subpopulations, the SCLC expansion cohorts will enroll additional subjects based on response to prior treatment and the number of previous therapies. Up to 250 second or third line subjects will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (75 second line subjects and 75 third line subjects treated with nivolumab 3 mg/kg every 2 weeks (Q2W)) or Arm B (50 second line subjects and 50 third line subjects treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens). Each arm will be limited

to 50% second line and 50% third line subjects to allow a meaningful subgroup evaluation for subjects with second-line versus third-line disease.

Two Stage Design: GC, PC, TNBC, or SCLC Arms N and N-I will follow a two-stage design to test whether nivolumab monotherapy or nivolumab combined with ipilimumab yields an objective response rate (ORR) that is of clinical interest in the investigated tumor types. For each tumor type, only treatment arms which meet an ORR threshold will proceed from Stage 1 to Stage 2 (described in protocol Section 3.2.2). Enrollment to Stage 2 in a given treatment arm can continue even if the other treatment arm is still in Stage 1. For TNBC and PC, the assessment of Dose Level 2b (nivolumab 3 mg/kg, ipilimumab 1 mg/kg) was assessed independently as a 2 Stage Design, regardless of efficacy results in the other dose cohorts.

For Stage 2, additional subjects will be assigned into Arm N, and Arm N-I up to a total of 100 subjects (including those assigned in Stage 1) in each treatment arm of the given tumor type. For tumor types where nivolumab monotherapy or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg proceeded to Stage 2, assessment of Dose Level 2b in Stage 2 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, n= up to 60 subjects) will be initiated for that tumor type. For SCLC, an additional 150 2L and 3L subjects (50% each) will be added in the nivolumab monotherapy arm, 100 2L and 3L subjects (50% each) will be added to N-I dose level 2.

Crossover for subjects in Arm N: Subjects in Arm N may crossover to Arm N-I if all of the following criteria are met:

- The Safety Evaluation Phase for the N-I regimen has been completed and at least 6 subjects have been exposed to the dose level used for Stage 1 of the N-I regimen. In case Dose Level 2b has been activated and completed the safety assessment, subjects for cross over will be assigned to Dose Level 2b.
- Subject has confirmed radiologic disease progression (investigator-assessed RECIST 1.1-defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression) in the absence of clinical deterioration. For subjects with clear evidence of new or progressing brain metastases a confirmation is not required. These subjects may proceed with brain radiation therapy and after having completed the radiation therapy a cross over to Arm N-I can be considered
- Subject has not experienced nivolumab related adverse events leading to permanent discontinuation.
- Subject is not continuing to derive any clinical benefit from nivolumab single agent therapy as assessed by the investigator which would allow continuation of nivolumab monotherapy.
- The individual case must be discussed with the medical monitor prior to cross over.

Subjects crossing over to Arm N-I will start treatment at Day 1 Week 1 as described for subjects originally assigned to Arm N-I. Subjects who cross over and subsequently have an objective response in Arm N-I will not be considered in the decision making for Arm N-I proceeding to Stage 2.

2.2 Treatment Assignment

The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document.

The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

Once enrolled in IVRS, enrolled subjects that have met all eligibility criteria will be ready for treatment assignment and drug vial assignment through the IVRS. The following information is required for drug vial assignment and randomization:

- Subject number
- Date of birth
- Tumor Type
- Date tumor tissue sample was shipped to central lab

Subjects meeting all eligibility criteria will be assigned to Arm N (nivolumab), or Arm N-I Dose Level 2 (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) or Arm N-I Dose Level 2b (nivolumab 3 mg/kg + ipilimumab 1 mg/kg) or Arm N-I Dose Level 2c (nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks) according to their tumor type and treatment arm availability:

- Within a given tumor type, subjects will be assigned to a treatment arm (N, or N-I Dose Level 2 or N-I Dose Level 2b) in a 1:1:1 ratio guided by randomization schedule if all arms are open.
- The computer-generated randomization schemas will be prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development.
- If only one or two treatment arms are open for enrollment (ie., when enrollment in Arm N-I is paused for an interim safety assessment, or when either arm is paused for decision making to proceed from Stage 1 to Stage 2 in the Efficacy Signal Detection part), then all newly to be assigned subjects will go into the remaining open arms.
- Once the subject has a treatment assignment, study treatment should be initiated within 3 working days.
- Specific instructions (including an enrollment worksheet) for central enrollment and treatment assignment procedure will be provided to the site.

Subjects to be enrolled in the SCLC expansion cohort will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects, nivolumab 3 mg/kg every 2 weeks (Q2W) or Arm B (100 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles

followed by nivolumab 3 mg/kg Q2W) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

Subjects to be enrolled in the OC expansion cohort will be randomized in a 1:1:1 ratio to one of 3 dose level groups:

- Arm A (40 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W)
- Arm B (40 subjects, nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W)
- Arm C (40 subjects, Nivolumab (3 mg/kg) Q2W + ipilimumab (1 mg/kg) Q6W)

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

Amendments 1 - 5 did not affect the statistical analysis. Amendment 07 is to update pharmacogenetics blood sample to include all current and future tumor types. Amendment 08 is to add nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg to the dose levels being investigated in study CA209-032, change the bladder cohort to a One Stage Design, and to add an optional external evaluation of CT or MRI scans for tumor types where data from study CA209-032 will potentially be used for future NDA submissions. Other changes were made to resolve minor inconsistencies and clarifications.

Amendment 09 includes:

- SCLC and Bladder: arms Nivo 3 mg/kg and Nivo 1/ Ipi 3 mg/kg, increase sample size.
- Updates to Blinded Independent Central Review (BICR) information
- Allowing brain radiation prior to cross over
- Allowing retreatment upon PD for patients with long lasting PR or CR and who had treatment held by investigator
- For the combination arm, subjects who meet discontinuation criteria will be allowed to continue with nivolumab treatment should the study related toxicities be attributed to ipilimumab. Ipilimumab would be discontinued.
- Updates to Primary, Secondary [redacted] Objectives
- Updates to Discontinuation criteria to include Grade 4 lymphocytopenia
- Updates to EQ-5D collection

Amendment 10 includes:

• Clarification regarding PK/immunogenicity sampling and pregnancy test was added.

• Regimen NI2c was added for treatment of ovarian cancer, including PK/immunogenicity and pregnancy sampling clarifications

• Safety assessments in all indications and treatment cohorts is harmonized: D4 W2 and W5 safety assessments are deleted from the NI cohorts consistent with nivolumab monotherapy and nivolumab 3 mg/kg Q2W/ipilimumab 1 mg/kg Q6W cohorts

• For options of treatment beyond progression and crossover to NI combination arm, specification of unequivocal disease progression based on non-target lesions only is added

• Specification of response to platinum-based therapy in SCLC and Ovarian cancer is added to appendices

• Regimen NI2c was removed from the flowchart for Bladder cancer (correction)

• For SCLC expansion cohort, clarification of stratified randomization is added

• For subjects from NI combination who undergo a re-exposure if they achieved an initial objective response (PR or CR) or stable disease of > 3 months and had a subsequent documented progression, an option to continue treatment with nivolumab monotherapy if ipilimumab treatment was stopped due to toxicity is added

3 OBJECTIVES

3.1 Primary

- To evaluate the objective response rate (ORR) of nivolumab monotherapy, or nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors. ORR will be assessed by a Blinded Independent Central Review (BICR) in selected tumor types.

3.2 Secondary

- To assess the safety of nivolumab monotherapy, or nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors.
- To assess Overall Survival (OS), OS-rate, Progression Free Survival (PFS), PFS-rate, and Duration of Response (DOR) with nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors. PFS and DOR will be assessed by a Blinded Independent Central Review (BICR) in selected tumor types.

- To characterize the immunogenicity of nivolumab monotherapy, or nivolumab and ipilimumab when combined.
- To evaluate the pharmacodynamic activity of nivolumab monotherapy, or nivolumab combined with ipilimumab in the peripheral blood and tumor tissue as measured by flow cytometry, immunohistochemistry, soluble factor analysis, and gene expression (microarray technology, quantitative RT-PCR).
- [redacted]

4 ENDPOINTS

4.1 Primary

4.1.1 Objective Response Rate

The primary endpoint is the objective response rate (ORR). The ORR is defined as the number of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of treated subjects. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of treatment assignment and the date of objectively documented progression per RECIST 1.1 or the start date of subsequent anti-cancer therapy, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan no less than 4 weeks after the criteria for response are first met. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

These measures of response will be interpreted in the context of historical responses observed following treatment with approved agents.

4.2 Secondary

The secondary objective (to assess the safety and tolerability of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic tumors) will be primarily assessed by the rate of treatment-related AEs leading to drug discontinuations during the first 12 weeks of treatment. In addition, safety and tolerability will be analyzed through the incidence of adverse events, serious adverse events, and specific laboratory abnormalities (worst grade) in each cohort. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

ORR will be further characterized by the duration of response (DOR) and the magnitude of reduction in tumor volume. DOR will be computed for subjects with a BOR of PR or CR and is defined as the time from first confirmed response (CR or PR) to the date of the first documented

tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored on the date of their last evaluable tumor assessment. Subjects who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessments prior to initiation of the subsequent anticancer therapy. The magnitude of reduction in tumor volume is defined as the percent decrease in tumor volume from baseline to nadir, observed up until the time of the first documented tumor progression or death.

Progression free survival (PFS) is defined as the time from first dosing date to the date of the first documented progression, as determined by the investigator or BICR for selected tumor type (per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who die without a reported progression or start of any subsequent anti-cancer therapy will be considered to have progressed on the date of their death. Subjects who did not progress or die will be considered as not progressed and will be censored on the date of their last evaluable assessment or last evaluable assessment prior to crossover. Subjects who did not have any on study assessments and did not die will be censored on the first dosing date. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable assessment prior to initiation of the subsequent anti-cancer therapy.

Table 4.2: Censoring scheme used in primary analysis of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments and no death	First Dosing date	Not Progressed
No on study tumor assessments and no death	First Dosing date	Not Progressed
Progression documented between scheduled visits	Date of the first documented tumor progression per RECIST 1.1	Progressed
Clinical progression without evidence of progression per RECIST 1.1 or No progression	Date of last tumor assessment with no documented progression or last evaluable assessment prior to crossover (for crossover subject without PD)	Not Progressed
New anticancer treatment started without a prior reported progression	Date of last tumor assessment prior or on the date of initiation of the subsequent anti-cancer therapy	Not Progressed
Death without progression per RECIST 1.1	Date of death	Progressed

OS is defined as the time between the first dosing date and the date of death due to any cause. A subject who has not died will be censored at the last known alive date. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

[redacted]

5 SAMPLE SIZE AND POWER

Sample size determination in the original protocol

This study comprises of a Dose Escalating Safety Evaluation Phase for the Combination Arm, followed by a Staged Enrollment for Arm N, and Arm N-I.

In the original protocol, gastric cancer, small cell lung cancer, triple negative breast cancer, and pancreatic cancer are included and the Staged Enrollment Part utilizes a modified Simon two-stage design with the treatment of 40 subjects to evaluate whether nivolumab, or the combination of nivolumab/ipilimumab yields an objective response rate (ORR) that is of clinical interest. In this study, an ORR of 10% or less is considered not of clinical value, and an ORR of 25% or greater is considered of strong clinical interest. The modified Simon design evaluates the null hypothesis that the true response rate is $\leq$ 10% versus the alternative hypothesis that the true response rate is > 10%. The 2-stage testing within each cohort targets a Type I error rate of 5% and has 80% power to reject the null hypothesis if the true response rate is 25%.

Sample size determination for bladder cancer cohort

In Amendment 06, bladder cohort is added. One stage design with the treatment of 60-100 subjects is used. These sample sizes provide 90% to 97% power to reject the null hypothesis of 10% response rate if the true response rate is 25% with a two-sided Type I error rate of 5%.

Sample size determination for SCLC expansion cohort

In Amendment 09, in addition to the original two-stage design of SCLC subjects, additional SCLC expansion cohort subjects will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects, nivolumab mono) or Arm B (100 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

Based on SCLC data so far observed in this study with an ORR of about 18% for nivolumab monotherapy, a sample size of N = 150 will target a Type I error rate of 5% and will have 84% power to reject the null hypothesis (ORR $\leq$ 10%) if the true response rate is 18%. An ORR of > 10% is considered a clinically meaningful result in a study population of second- and third-line SCLC patients.

Based on SCLC data so far observed in this study with an ORR of about 30% for nivolumab / ipilimumab combination therapy, a sample size of N = 100 will target a Type I error rate of 5% and will have 83% power to reject the null hypothesis (ORR $\leq$ 18%) if the true response rate is

30%. An ORR of > 18% is considered a clinically meaningful result for a nivolumab / ipilimumab combination in a study population of second- and third-line SCLC patients which outweighs the potential for higher toxicity to be anticipated for this cohort.

Sample size determination for ovarian cancer cohort

Also in Amendment 09, ovarian cancer cohort is added and one stage design with the treatment of 40 subjects for each arm will be used. These sample sizes will provide 79% power to reject the null hypothesis of 10% response rate if the true response rate is 25% with a two-sided Type I error rate of 5%.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 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.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline.

6.1.2 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). An AE will be counted as on-treatment if the event occurred within 30/100 days of the last dose of study treatment.

On-treatment evaluations (laboratory tests, pulse oximetry, and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30/100 days of the last dose of study treatment.

6.2 Treatment Regimens

The treatment group "**as assigned"** will be retrieved from the IVRS system

The treatment group "**as treated**" will be the same as the arm as assigned 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

- Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- Assigned Subjects: All subjects who were assigned to the highest tested tolerated dose level in the Dose Escalating Safety Evaluation Phase or to any treatment group during the Staged Enrollment Phase.
- All Treated Subjects: All subjects who received at least one dose of any study medication.
- All Response Evaluable Subjects: A subject will be part of the response evaluable subject if the following criteria are met:
  - a) BOR is in (CR, PR, SD or PD),
  - b) at least one target lesion identified at baseline,
  - c) at least at one on-study timepoint with target lesion assessment (non missing percent change from baseline).
- All PK Subjects: All assigned subjects with available serum time-concentration data.
- Immunogenicity Subjects: All treated subjects with baseline and at least 1 post baseline immunogenicity assessment.
- Crossover Subjects: All treated subjects who crossed over from Arm N to Arm N-I.
- All PD-L1 tested subjects: All subjects who had a tumor tissue sample available for assessment of PD-L1 expression at baseline.
- All Treated PD-L1 tested subjects: All PD-L1 tested subjects who received at least one dose of study treatment.
- PD-L1 evaluable subjects: All treated, PD-L1 tested subjects with quantifiable PD-L1 expression.

7 STATISTICAL ANALYSES

7.1 General Methods

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

Time to event distributions (i.e. overall survival, progression free survival, time to response, and duration of response) will be estimated using Kaplan Meier techniques. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology (using the log-log transformation for construction of confidence intervals). Rates at fixed timepoints (e.g. OS at 12 months) will be derived from the Kaplan Meier estimate along with their

corresponding log-log transformed 95% confidence intervals. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

7.2 Study Conduct

7.2.1 Accrual

The following will be presented on the enrolled population:

- Number of subjects accrued by country and investigational site
- Number of subjects accrued by month

7.2.2 Relevant Protocol Deviations

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

At Entrance:

- Subjects with baseline ECOG performance status > 1
- Subjects without measurable disease at baseline

On-study:

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

Listings will also be provided.

7.3 Study Population

7.3.1 Subject Disposition

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

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

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

A subject list for all treated subjects will be provided showing the subject's randomization date, first and last dosing date, off study date and reason for going off-study.

7.3.2 Demographics and Baseline Characteristics

The following baseline characteristics will be summarized by cohort for all treated subjects. All baseline presentations identify subjects with missing measurements. In tabulations of categorical variables, percents are based on subjects with measurements. Listings will also be provided.

- Age (descriptive statistics)
- Age category (< 65, ≥ 65 - < 75, ≥ 75 - < 85, ≥ 65, ≥ 75, ≥ 85)
- Gender (male/female)
- Race (white/black/asian/other)
- Region (US, Europe)
- ECOG Performance Status (0/1)
- Weight (descriptive statistics)
- Baseline LDH (≤ULN, >ULN)
- Baseline LDH (≤2*ULN, >2*ULN)
- History of Brain Metastases (Yes/No)
- Baseline liver metastases (yes/no)
- Baseline visceral metastases (lung, liver and bone) (yes/no)
- Baseline lymph node only (yes/no)
- Baseline Hemoglobin (< 10g/dL vs. ≥ 10g/dL)
- Baseline Creatinine Clearance (CrCL) (< 30, 30 - < 60, ≥ 60ml/min)

The creatinine clearance will be calculated using Cockroft-Gault formula, defined as:

Formula 1:

$$\text{CrCL(ml/min)} = \frac{(140 - \text{age (in years)}) * \text{weight (in kg)}}{72 * \text{serum creatinine (in mg/dL)}}$$

for males and

Formula 2:

$$\text{CrCL(ml/min)} = \frac{(140 - \text{age (in years)}) * \text{weight (in kg)}}{72 * \text{serum creatinine (in mg/dL)}} * 0.85$$

for females. Baseline weight will be used.

- Time from Initial Disease Diagnosis to Assignment (<1 year,1-<2 year, 2-<3 year,3-<4 year, 4-<5 year, ≥5 year)
- All lesions (Investigator Tumor Assessments at Baseline): sites of disease, number of disease sites per subject
- Target lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of longest diameter of target lesion
- Platinum resistant/refractory versus platinum sensitive (SCLC only) and Platinum-refractory versus platinum resistant vs platinum sensitive (OC only)
- Smoking status (SCLC only)

7.3.3 Medical History

General medical history will be listed by subject.

7.3.4 Prior Therapy

The following will be summarized by cohort for the all treated population.

- Prior neo-adjuvant therapy (yes/no)
- Prior adjuvant therapy (yes/no)
- Time from completion of prior adjuvant therapy to assignment (subjects who received prior adjuvant therapy), (< 6 months and >= 6 months)
- Prior surgery related to cancer (yes/no)
- Prior radiotherapy (yes/no)
- Number of prior therapies received (2, 3, >=4)
- Best response to most recent prior regimen (CR/PR vs SD vs PD)
- For SCLC cohort: Time from first line treatment to start of second line treatment (<= 90 days and > 90 days)
- Prior platinum experience (cisplatin only, carboplatin only, both or other) by setting
- Characteristics of the most recent prior platinum regimen associated with recurrence/progression: Best response, reason off-treatment and time from last dose to recurrence/progression
- Time from completion of most recent prior regimen to study treatment (< 3, 3 - < 6, ≥ 6 months)

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, treatment group, and tumor type for all treated subjects.

7.4 Extent of Exposure

Analyses in this section will be performed in all treated subjects.

For the analyses of crossover subjects during original assigned treatments, the exposure will be truncated at the first crossover dose date. All others will follow regular counting rules. For the analysis of crossover subjects during crossover period, the exposure will be started at the first crossover dose date.

7.4.1 Administration of Study Therapy

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

- Relative dose intensity (%) using the following categories: <50%; 50 - <70%; 70 - <90%; 90 - <110%, ≥110%.
- Number of doses of nivolumab, ipilimumab (summary statistics)
- Cumulative dose of nivolumab, ipilimumab

Duration of treatment will be presented by cohort 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 extent of exposure (weight, number of doses, date of first and last dose, cumulative dose, relative dose intensity, duration of treatment, and reason for discontinuation) will be provided.

Table 7.4.1-1: Study Therapy Parameter Definitions

	Nivolumab in Arm N and Arm N-I Dose Level 2c	Nivolumab in Arm N-I Dose Levels 1, 2 and 2b	Ipilimumab in Arm N-I Dose Levels 1, 2, 2b, and 2c
Dosing Schedule per Protocol	3 mg/kg every 2 weeks	1 or 3 mg/kg every 3 weeks for 4 doses followed by 3 mg/kg every 2 weeks OR Maximum tolerable dose identified in escalation phase. MTD may differ by tumor type	1 or 3 mg/kg 3 weeks for 4 doses or 1mg/kg 6 weeks (2c)
Dose	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)
Cumulative Dose	Cum Dose (mg/kg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.
Dose Intensity (%)	7x Cum dose/(Last dose date - Start dose date + 14)	For Combo phase (the first two cycles): 7x Cum dose in Combo phase /(Last dose date in Combo phase- Start dose date + 21) For Mono phase (cycle 3 and beyond): 7x Cum dose in Mono phase /(Last dose date - Start dose date in Mono phase + 14)	7 x Cum dose/(Last dose date - Start dose date + 21) For 2c: 7 x Cum dose/(Last dose date - Start dose date + 42)
Relative Dose Intensity (%)	Cum dose /[(Last dose date - Start dose date + 14) x 3/14] x 100	Cum dose/[(3 or 1) x (Last dose date - Start dose date + 21)/21] x 100, if the last dose is in Combo phase Cum dose/[(3 or 1) x 4 + 3 x (Last dose date - 84 + 14)/14] x 100, if the last dose is in Mono phase	Cum dose/[(3 or 1) x (Last dose date - Start dose date + 21)/21] x 100 For 2c: Cum dose/[(1) x (Last dose date - Start dose date + 42)/42] x 100
Duration of Treatment	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*

Volume infused, volume prepared, and weight are collected on the CRF. Nominal nivolumab dose collected in IVRS. i = 1, 2,...,N, where N = number of infusions. Cycle Duration $_{(N)}$ = 3 weeks for nominal 1or 3 mg/kg nivolumab doses and 2 weeks for nominal 3 mg/kg. Intended dose per week is .33 or 1 mg/kg

for nominal 1or 3 mg/kg nivolumab doses and 1.5 mg/kg for nominal 3 mg/kg nivolumab doses. If different from the above dosing, the MTD will be used for ARM N-I and may vary by tumor type.

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 cohort:

- Number of dose delays per subject, length of delay (4 - <8 days, 8 - <15 days, 15- <42 days, ≥ 42 days), 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 cohort:

- Number of subjects with at least one dose infusion interruption, the reason for interruption, and the number of infusion interruptions per subject.
- Number of subjects with at least one IV infusion rate reduction and the reason for reduction.

7.4.2.3 Dose Escalations

Dose escalations are not permitted for either nivolumab or ipilimumab.

7.4.2.4 Dose Reductions

Dose reductions are not permitted for either nivolumab or ipilimumab.

7.4.2.5 Dose Omissions

Dose omissions are not permitted for either nivolumab or ipilimumab.

7.4.3 Administration and Modifications of Study Therapy Post Crossover

The following parameters will be summarized (descriptive statistics) based on exposure data collected in treated crossover subjects on or after the first date of active ipilimumab therapy.

- Number of ipilimumab and nivolumab doses received post crossover.
- Cumulative ipilimumab and nivolumab dose post crossover.
- Relative ipilimumab and nivolumab dose intensity (%) post crossover using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- Number of ipilimumab and nivolumab dose delays post crossover per subject, length of delay, and reason for delay.
- Number of subjects with at least one dose infusion interruption post crossover, the reason for interruption, and the number of infusion interruptions per subject.
- Number of subjects with at least one IV infusion rate reduction post crossover and the reason for reduction.

[redacted]

7.5 Efficacy

Efficacy analyses will be performed on all treated subjects, except where otherwise indicated.

7.5.1 Objective Response Rate

7.5.1.1 Primary Analysis

ORR will be summarized for each cohort by a binomial response rate and corresponding two-sided 95% exact CI using the method proposed by Atkinson and Brown[1] for cohorts using two-stage design and Clopper and Pearson method for cohorts using one stage design.

DOR will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier product-limit method. Median values of DOR, along with two-sided 95% CI using the log-log transformation will also be calculated by cohort. In addition, the percentage of responders still in response at different time points (3, 6, and 12 months) will be presented based on the KM plot.

For SCLC expansion cohorts, similar methods will be used to summarize ORR and DOR for each stratification factor.

The magnitude of reduction in tumor burden will be summarized descriptively.

For the analyses of crossover subjects during original assigned treatments, ORR data will be truncated prior to the first crossover dose date. For the analysis of crossover subjects during crossover period, ORR will also be summarized. Baseline will be re-established. BOR, PR, and CR will be re-derived starting on the date of crossover.

In addition, percent change from baseline based on the target lesions will be plotted overtime for each subject grouped by treatment arm (spider plot). For crossover subjects, data will be truncated prior to the first date of crossover.

Time on therapy and time to response will also be plotted for each subject with symbols indicating time of radiographic progression, LKDA, first response, last dose, last dose when subject off treatment, crossover, and death (swimmer plot). For crossover subjects, no data will be truncated.

- A plot of individual time course of tumor burden change per investigator assessment but limited to subjects who were treated beyond progression.

Among subjects treated beyond progression, non-conventional benefiters will be identified and will be defined as subjects who had not experienced a BOR of PR/CR prior to initial RECIST-defined progression, and met at least one of the following:

- Criterion 1: Appearance of a new lesion followed by decrease from baseline of at least 10% in the sum of the target lesions.
- Criterion 2: Initial increase from nadir ≥ 20% in the sum of the target lesions followed by reduction from baseline of at least 30%.
- Criterion 3: Initial increase from nadir ≥ 20% in the sum of the target lesions or appearance of new lesion followed by at least 2 tumor assessments showing no further progression defined as a 10% additional increase in sum of target lesions and new lesions.

7.5.2 Progression Free Survival

7.5.2.1 Primary Analysis

The PFS curves for each cohort will be estimated using the KM product-limit method. Two-sided, 95% confidence intervals for median PFS will be computed using the log-log transformation.

PFS rates at 3, 6, and 12 months will be estimated using KM estimates on the PFS curve for each cohort. Minimum follow-up must be longer than the timepoint to generate the rate. The associated two-sided 95% CI will also be calculated.

The source of progression (death vs. progression) will be summarized.

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

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

7.5.2.2 Sensitivity Analysis

Sensitivity analyses of PFS will also be performed using the following modification:

- PFS accounting for assessment on/after subsequent therapy. PFS will be defined similarly to the primary analysis except that events (progression or death) and tumor assessments that occurred on or after subsequent anti-cancer therapy will be taken into account.

7.5.3 Overall Survival

OS curves for each cohort will be estimated using the Kaplan-Meier (KM) product limit method. Median OS and the corresponding two-sided 95% confidence intervals using the log-log transformation will be computed. Survival rates at 3, 6, 12, 18, 24, 36, 48, and 60 months will be estimated using KM estimates on the OS curve for each cohort. Minimum follow-up must be longer than the timepoint to generate the rate. Associated two-sided 95% CIs will be calculated.

For crossover subjects, no data will be truncated.

7.5.3.1 Subject Follow-up

The extent of follow-up defined as the time between assignment 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 assigned subjects.

The currentness of follow-up, 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 cohort. Subjects who died and subjects with a Last Known Date Alive on or after LPLV will have a value of '0' for currentness of follow-up. The currentness of follow-up will be categorized into the following categories: 0 days, 1-30 days, 31-60 days, 61-90 days, 91-120 days, 120-150 days, 151 or more days.

7.5.3.2 Subsequent Therapy

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

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

A by-subject listing of follow-up therapy will be produced for subjects who had any subsequent therapy.

7.5.4 Interim Analyses

Data will be reviewed during the Dose Escalation Safety Evaluation Phase to determine the maximum tolerated dose level for arm N-I and to make decisions about Stage 2 for each cohort. The decision to proceed from Stage 1 to Stage 2 will be conducted for TNBC, GC, PC, and SCLC treatment arms with two-stage design independently.

Interim analyses may be conducted after Stage 1, by cohort. These interim analyses may be triggered if a "super" response (i.e. 8 or more responders out of 18 subjects) is observed or if it is necessary in order to make decisions regarding further development and supporting external disclosure such as medical conference. Summaries and listings of efficacy and safety will be provided. This interim analysis will not impact the study duration and the trial will continue as planned.

For BC and OC cohorts, one-stage design is used. The interim analysis will be conducted by cohort to support internal decision making and publication disclosure.

For new SCLC expansion cohorts, no interim analysis will be performed.

7.6 Safety

For all safety related analyses, refer to the Core Safety SAP[2]. Safety will be summarized for: all treated subjects, by cohort; all dose escalation subjects, by tumor type; and all crossover subjects, by tumor type.

For the analyses of crossover subjects during original assigned treatments, all the AE will be truncated at the first crossover dose date. All others will follow regular counting rules. For the analysis of crossover subjects during crossover period, all the AE will be counted at the first crossover dose date.

7.6.1 Deaths

See Core Safety SAP.

7.6.2 Serious Adverse Events

See Core Safety SAP.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP.

7.6.4 Adverse Events Leading to Dose Delay of Study Therapy

See Core Safety SAP.

7.6.5 Adverse Events

See Core Safety SAP.

7.6.6 Select Adverse Events

See Core Safety SAP.

7.6.7 Immune Modulating Medication

See Core Safety SAP.

7.6.8 Multiple Events

See Core Safety SAP.

7.6.9 Clinical Laboratory Evaluations

7.6.9.1 Hematology

See Core Safety SAP.

7.6.9.2 Serum Chemistry

See Core Safety SAP.

7.6.10 Immunogenicity

See Core Safety SAP.

7.6.11 Vital Signs and Pulse Oximetry

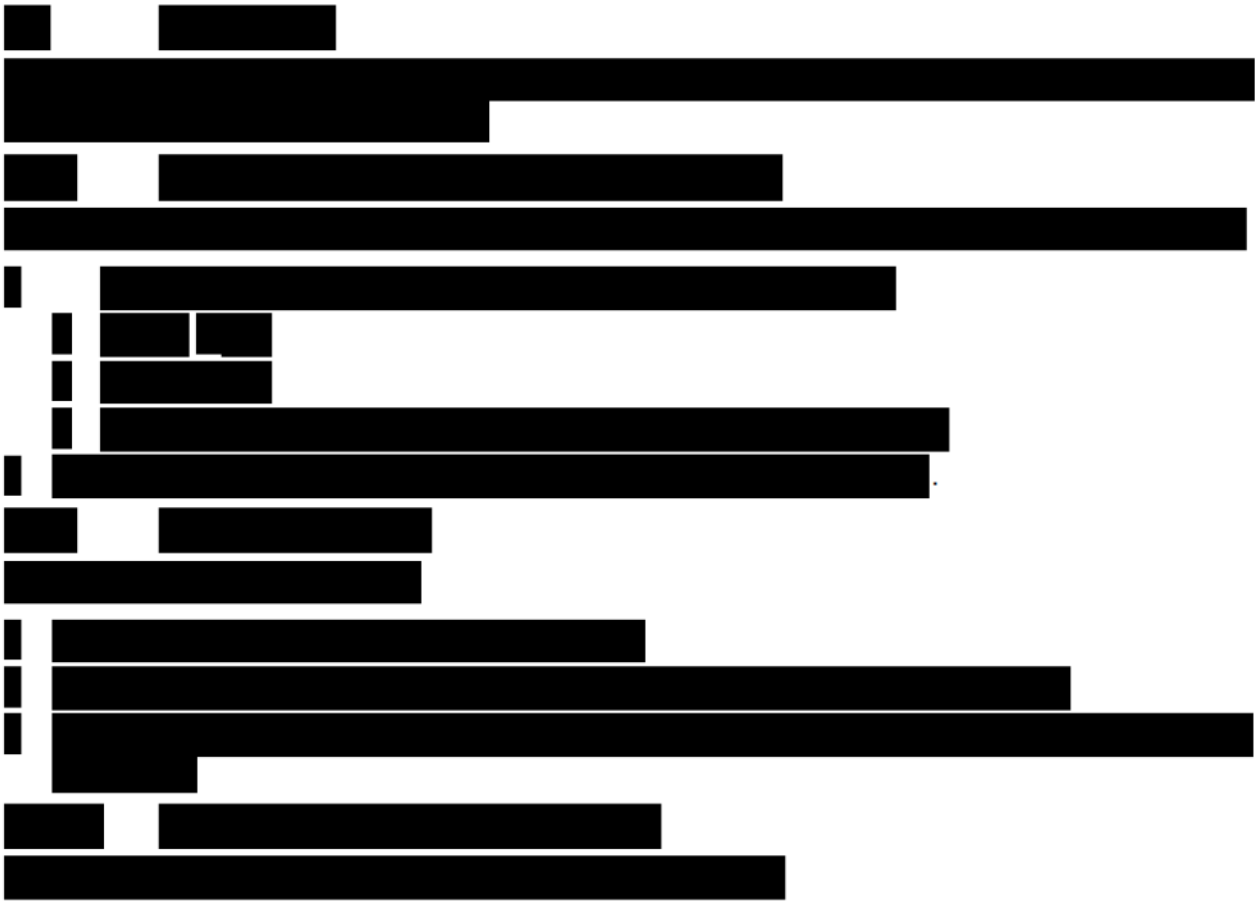
See Core Safety SAP.

7.7 Pregnancy

See Core Safety SAP.

7.8 Pharmacokinetics

Summary statistics will be calculated for nivolumab and ipilimumab concentrations, and summarized by scheduled sample collection time. The nivolumab concentration 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. In addition, exposure-response analyses with selected efficacy and safety endpoints will be conducted. Results of population PK and exposure response-analyses will be reported separately.



[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[3]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[4].

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 day 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 day
- 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 day

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

*In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions may be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

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

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

Duration = (Last date - first date + 1)

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 described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

[redacted]

STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT - SCLC EXPANSION COHORT

A PHASE 1/2, OPEN-LABEL STUDY OF NIVOLUMAB MONOTHERAPY OR NIVOLUMAB COMBINED WITH IPILIMUMAB IN SUBJECTS WITH ADVANCED OR METASTATIC SMALL CELL LUNG CANCER (SCLC)

PROTOCOL CA209032

VERSION # 1.0

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[redacted]

2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 1/2, open-label study of nivolumab monotherapy (Arm N), or nivolumab combined with ipilimumab (Arm N-I) in adult (≥ 18 years) subjects with advanced or metastatic SCLC. Subjects will be assigned to one of the following treatment arms:

Arm N: Nivolumab monotherapy (3 mg/kg) Q2W

Arm N-I Dose Level 1: Nivolumab (1 mg/kg) + Ipilimumab (1 mg/kg) Q3W for 4 doses, then Nivolumab (3 mg/kg) Q2W

Arm N-I Dose Level 2: Nivolumab (1 mg/kg) + Ipilimumab (3 mg/kg) Q3W for 4 doses, then Nivolumab (3 mg/kg) Q2W

Arm N-I Dose Level 2b: Nivolumab (3 mg/kg) + Ipilimumab (1 mg/kg) Q3W for 4 doses, then Nivolumab (3 mg/kg) Q2W

SCLC Pre-Expansion Cohort:

Dose-Escalation Safety Evaluation Phase for Combination Arm: Although the regimen used in the phase 3 melanoma study, novolumab 1 mg/kg + ipilimumab 3 mg/kg, was expected to also be tolerable in the tumor studied here, an initial dose-escalating safety evaluation for the combination arms was conducted for the SCLC pre-expansion cohort.

Enrollment to Stage 1 for Arm N occurred in parallel to the safety evaluation for Arm N-I.

Two Stage Design: SCLC Arms N and N-I followed a two-stage design to test whether nivolumab monotherapy or nivolumab combined with ipilimumab yield an objective response rate (ORR) that is of clinical interest. Only treatment arms which met an ORR threshold proceeded from Stage 1 to Stage 2 (described in protocol Section 3.1.3). Enrollment to Stage 2 in a given treatment arm continued even if the other treatment arm was still in Stage 1.

For Stage 2, additional subjects were assigned into Arm N, and Arm N-I up to a total of 100 subjects (including those assigned in Stage 1) in each treatment arm. Assessment of Dose Level 2b in Stage 2 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, n= up to 70 subjects) were initiated when nivolumab monotherapy or nivolumab 1 mg/kg + ipilimumab 3 mg/kg proceeded to Stage 2.

Crossover for subjects in Arm N: Subjects in SCLC pre-expansion cohort Arm N were permitted to crossover to Arm N-I if all of the following criteria were met:

- The Safety Evaluation Phase for the N-I regimen had been completed and at least 6 subjects had been exposed to the dose level used for Stage 1 of the N-I regimen. In case Dose Level 2b had been activated and completed the safety assessments, subjects for crossover were assigned to Dose Level 2b.
- Subject had further disease progression (investigator-assessed RECIST 1.1-defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression) in the absence of clinical deterioration. For subjects with clear evidence of new or progression brain metastases a confirmation was not required. These subjects were permitted to proceed with brain radiation therapy and after having completed the radiation therapy a crossover to Arm N-I was considered.
- Subjects with rapidly progressing tumors under nivolumab monotherapy were permitted to undergo radiation treatment first before initiation of the crossover after discussion between the sponsor and investigator.
- Subject did not experience nivolumab related adverse events leading to permanent discontinuation.
- Subject did not continue to derive any clinical benefit from nivolumab single agent therapy as assessed by the investigator which would allow continuation of nivolumab monotherapy.
- The individual case was to be discussed with the medical monitor prior to crossover.

Subjects who crossed over to Arm N-I started treatment at Day 1 Week 1 as described for subjects originally assigned to Arm N-I. Subjects who crossed over and subsequently had an objective response in Arm N-I were not considered in the decision making for Arm N-I proceeding to Stage 2.

SCLC Expansion:

SCLC pre-expansion cohort Arm N and Arm N-I met the pre-specified safety and efficacy criteria and proceeded to Stage 2. Based on an interim data review, disease control rates (SD + PR + CR) of 36% and 57% for Arms N and N-I, respectively, were estimated.

In order to further investigate nivolumab and nivolumab combined with ipilimumab activity in specific SCLC subpopulations, the SCLC expansion cohorts will enroll additional subjects based on response to prior treatment and the number of previous therapies. Up to 250 second or third line subjects will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (75 second line

subjects and 75 third line subjects treated with nivolumab 3 mg/kg every 2 weeks (Q2W)) or Arm B (50 second line subjects and 50 third line subjects treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens). Each arm will be limited to 50% third line subjects to allow a meaningful subgroup evaluation for subjects with second-line versus third-line disease. The crossover from Arm N to Arm N-I dose level 2 is not allowed for the SCLC expansion cohort.

Although crossover was not to be permitted for the SCLC expansion cohort, the interim results for the SCLC cohorts showed that two subjects in the SCLC expansion cohort crossed over; therefore, the handling of crossover subjects is described below for consistency.

2.2 Treatment Assignment

The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document.

The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

Once enrolled in IVRS, enrolled subjects that have met all eligibility criteria will be ready for treatment assignment and drug vial assignment through the IVRS. The following information is required for drug vial assignment and randomization:

- Subject number
- Date of birth
- Tumor Type
- Date tumor tissue sample was shipped to central lab

Subjects to be enrolled in the SCLC expansion cohort will be randomized in a 3:2 ratio to one of 2 expansion groups: nivolumab monotherapy arm (150 subjects, nivolumab 3 mg/kg every 2 weeks (Q2W) or N-I dose level 2 arm (100 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 cycles followed by nivolumab 3 mg/kg Q2W) and will be stratified for number of prior treatment lines (1 vs 2 or more prior chemotherapy regimens).

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

All protocol amendments related to the SCLC cohort are included below.

Amendments 1-5 did not affect the statistical analysis.

Amendment 07 is to update pharmacogenetics blood sample to include all current and future tumor types.

Amendment 08 is to add nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg to the dose levels being investigated in study CA209-032, and to add an optional external evaluation of CT or MRI scans.

Amendment 09 includes:

- SCLC: arms nivolumab 3 mg/kg and nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg, increase sample size.
- Updates to Blinded Independent Central Review (BICR) information.
- Allowing brain radiation prior to crossover.
- Allowing retreatment upon PD for patients with long lasting PR or CR and who had treatment held by investigator.
- For the combination arm, subjects who meet discontinuation criteria will be allowed to continue with nivolumab treatment should the study related toxicities be attributed to ipilimumab. Ipilimumab would be discontinued.
- Updates to Primary, Secondary [redacted] Objectives.
- Updates to Discontinuation criteria to include Grade 4 lymphocytopenia.
- Updates to EQ-5D collection.

Amendment 10 includes:

- Clarification regarding PK/immunogenicity sampling and pregnancy test was added.
- Safety assessments in all indications and treatment cohorts is harmonized: D4 W2 and W5 safety assessments are deleted from the NI cohorts consistent with nivolumab monotherapy.
- For options of treatment beyond progression and crossover to NI combination arm, specification of unequivocal disease progression based on non-target lesions only is added.
- Specification of response to platinum-based therapy in SCLC is added to appendices.
- For SCLC expansion cohort, clarification of stratified randomization is added.
- For subjects from NI combination who undergo a re-exposure if they achieved an initial objective response (PR or CR) or stable disease of > 3 months and had a subsequent documented progression, an option to continue treatment with nivolumab monotherapy if ipilimumab treatment was sopped due to toxicity is added.

Amendment 11 includes:

- Clarification regarding the local lab assessment timing was added.
- For SCLC expansion cohort, exact language regarding number of prior treatment lines added for consistency with Section 3.1.5 of the protocol and the study synopsis.
- Specification of the crossover option: this option refers only to the original cohorts and not the new cohorts enrolled under or after Amendment 09 implementation.
- To increase flexibility in obtainment of tumor samples, for subjects with only one site of measurable disease tumor sampling criteria for biopsies from NOT the only site of measurable disease were widened.
- Clarification regarding requirement for baseline CT and MRI brain scans.
- [redacted]

Amendment 12:

- Changed the primary objective for the expansion SCLC cohort to require evaluation by BICR.
- Removed the limitation of enrolling subjects with 1 or 2 prior lines of therapy in the same fixed proportion of 50% for each subgroup.
- Added permission to use palliative radiation therapy to other non-target lesions.
- Added permission to use surgical resection or stereotactic radiotherapy following initial response or long-term stable disease.
- Limited PK and immunogenicity samples collection up to 2 years.
- Updated Appendix 2 of protocol (Management Algorithms) to reflect updates in the nivolumab IB.
- Updated Appendix 6 of protocol (Methods of Contraception) to reflect updates in the nivolumab IB.

Amendments 13-16 were not related to the SCLC cohort.

3 OBJECTIVES

Only objectives pertinent to the SCLC Expansion Cohort will be covered in this SAP. Other objectives are covered in a separate statistical analysis plan.

3.1 Primary

SCLC Expansion Cohort:

- To compare the objective response rate (ORR) as assessed by a Blinded Independent Central Review (BICR) for nivolumab monotherapy versus nivolumab combined with ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg).

3.2 Secondary

- To assess the safety of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic SCLC.
- To assess overall survival (OS), OS rate, progression-free survival (PFS), PFS rate, and duration of response (DOR) for subjects treated with nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic SCLC. PFS and DOR will be assessed by a Blinded Independent Central Review (BICR).

[redacted]

4 ENDPOINTS

4.1 Primary

4.1.1 Objective Response Rate

The primary endpoint is the objective response rate (ORR). The ORR is defined as the number of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of treated subjects. The BOR is defined as the best response designation, as determined by the investigator or BICR, recorded between the date of treatment assignment and the date of objectively documented progression per RECIST 1.1 or the start date of subsequent anti-cancer therapy, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan no less than 4 weeks after the criteria for response are first met. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

4.2 Secondary

The secondary objective (to assess the safety and tolerability of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic SCLC) will be

primarily assessed by the rate of treatment-related AEs leading to drug discontinuations during the first 12 weeks of treatment. In addition, safety and tolerability will be analyzed through the incidence of adverse events, serious adverse events, and specific laboratory abnormalities (worst grade). Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

ORR will be further characterized by the duration of response (DOR) and the magnitude of reduction in tumor volume. DOR will be computed for subjects with a BOR of PR or CR and is defined as the time from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored on the date of their last evaluable tumor assessment. Subjects who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. The magnitude of reduction in tumor volume is defined as the percent decrease in tumor volume from baseline to nadir, observed before the time of the first documented tumor progression or death.

Progression free survival (PFS) is defined as the time from first dosing date to the date of the first documented progression, as determined by the investigator or BICR (per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who die without a reported progression or start of any subsequent anti-cancer therapy will be considered to have progressed on the date of their death. Subjects who did not progress or die will be considered as not progressed and will be censored on the date of their last evaluable assessment or last evaluable assessment prior to crossover. Subjects who did not have any on study assessments and did not die will be censored on the first dosing date. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable assessment prior to initiation of the subsequent anti-cancer therapy. Please refer to Table 4.2-1 for the censoring scheme in primary analysis of PFS.

Table 4.2-1: Censoring scheme used in primary analysis of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments and no death	First dosing date	Not Progressed
No on study tumor assessments and no death	First dosing date	Not Progressed
Progression documented between scheduled visits	Date of the first documented tumor progression per RECIST 1.1	Progressed
Clinical progression without evidence of progression per RECIST 1.1 or No progression	Date of last tumor assessment with no documented progression or last evaluable assessment prior to crossover (for crossover subject without PD)	Not Progressed

Table 4.2-1: Censoring scheme used in primary analysis of PFS

Situation	Date of Progression or Censoring	Outcome
New anticancer treatment started without a prior reported progression	Date of last tumor assessment prior or on the date of initiation of the subsequent anti-cancer therapy	Not Progressed
Death without progression per RECIST 1.1	Date of death	Progressed

OS is defined as the time between the first dosing date and the date of death due to any cause. A subject who has not died will be censored at the last known alive date. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

Sample size determination for SCLC expansion cohort

In Amendment 09, in addition to the original two-stage design of SCLC subjects, additional SCLC expansion cohort subjects will be randomized in a 3:2 ratio to one of 2 expansion groups: Arm A (150 subjects, nivolumab mono) or Arm B (100 subjects, nivolumab 1 mg/kg + ipilimumab 3 mg/kg) and will be stratified for number of prior treatment lines (1 vs 2 prior chemotherapy regimens).

Based on SCLC data so far observed in this study with an ORR of about 10% for nivolumab monotherapy and about 23% for nivolumab / ipilimumab combination therapy, sample sizes of N = 150 for nivolumab monotherapy and N = 100 for nivolumab / ipilimumab combination therapy (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) will target a Type I error rate of 5% (two-sided) and will have 78% power to detect the difference between these two arms, if the true ORR rates are 10% and 23%, respectively.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 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.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definition will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will be considered as baseline.

6.1.2 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). An AE will be counted as on-treatment if the event occurred within 30/100 days of the last dose of study treatment.

On-treatment evaluations (laboratory tests, pulse oximetry, and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30/100 days of the last dose of study treatment.

6.2 Treatment Regimens

The treatment group "**as assigned**" will be retrieved from the IVRS system.

The treatment group "**as treated**" will be the same as the arm as assigned 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

As noted previously, this SAP describes analyses for the SCLC expansion cohort as well as the SCLC pooled pre-expansion and expansion cohorts; therefore, for the descriptions provided below, "subjects" refers to "subjects with SCLC - Expansion Cohort" and "subjects with SCLC" where applicable.

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- All Randomized Subjects: All subjects who were randomized to any treatment arm in the SCLC Expansion Cohort.
- All Treated Subjects: All subjects who received at least one dose of any study medication.
- All Response Evaluable Subjects: A subject will be part of the response evaluable subject if the following criteria are met:
    a) BOR is in (CR, PR, PD or SD),
    b) at least one target lesion identified at baseline,
    c) at least one on-study timepoint with target lesion assessment (non missing percent change from baseline).
- All PK Subjects: All assigned subjects with available serum time-concentration data.
- All Immunogenicity Subjects: All treated subjects with baseline and at least 1 post baseline immunogenicity assessment.
- All PD-L1 Tested Subjects: All subjects who had a tumor tissue sample available for assessment of PD-L1 expression at baseline.
- All Treated, PD-L1 Tested Subjects: All PD-L1 tested subjects who received at least one dose of study treatment.
- PD-L1 Evaluable Subjects: All treated, PD-L1 tested subjects with quantifiable PD-L1 expression.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, analyses outlined in Sections 7.2 through 7.5 and Section 7.9 will be performed using the SCLC expansion cohort treated with nivolumab monotherapy or with nivolumab in combination with ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg). Safety will be summarized for all treated subjects in the SCLC pooled pre-expansion and expansion cohorts, by treatment group (nivolumab and nivolumab 1 mg/kg + ipilimumab 3 mg/kg). All listings will be produced for the SCLC pooled pre-expansion and expansion cohorts.

The following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category, for the SCLC expansion cohort. Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized for the expansion cohort using the mean, standard deviation, median, minimum and maximum values.

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

median along with 95% CI will be provided using Brookmeyer and Crowley methodology (using the log-log transformation for construction of confidence intervals). Rates at fixed timepoints (e.g. OS at 12 months) will be derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% confidence intervals. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

7.2 Study Conduct

7.2.1 Accrual

The following will be presented on the enrolled population for all treatment groups:

- Number of subjects accrued by country and investigational site
- Number of subjects accrued by month

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and summarized for the SCLC expansion cohort (including nivolumab and nivolumab 1 mg/kg + ipilimumab 3 mg/kg treatment groups). Non-programmable relevant eligibility and on-treatment deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

At Entrance:

- Subjects with baseline ECOG performance status > 1
- Subjects without measurable disease at baseline

On-study:

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

Listings will also be provided.

7.3 Study Population

7.3.1 Subject Disposition

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

Number of subjects who discontinued study treatment along with the 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.

Number of subjects randomized but not treated along with the reason, will be tabulated by treated group as assigned. This analysis will be performed on the All Randomized Subjects population.

A subject listing for All Treated Subjects will be provided showing the subject's first and last dosing date, off study date and reason for going off-study.

7.3.2 Demographics and Baseline Characteristics

The following baseline characteristics will be summarized for all treated subjects by treatment group for the expansion cohort. All baseline presentations identify subjects with missing measurements. In tabulations of categorical variables, percent is based on subjects with measurements. Listings will also be provided.

- Age (descriptive statistics)
- Age category (< 65, ≥ 65 - < 75, ≥ 75, ≥ 65)
- Gender (male/female)
- Race (white/black/asian/other)
- Ethnicity (Hispanic or Latino/Not Hispanic or Latino)
- Region (US, Europe, Rest of World)
- Number of Prior Lines of Therapy (0, 1, 2-3, 4-5, >5)
- ECOG Performance Status (0/1)
- Weight (descriptive statistics)
- Baseline LDH (≤ULN, >ULN)
- Baseline LDH (≤2*ULN, >2*ULN)
- History of brain mestastases (yes/no)
- Baseline liver mestastases (yes/no)
- Baseline visceral mestastases (lung, liver and bone) (yes/no)
- Baseline lymph node only (yes/no)
- Baseline hemoglobin (< 10g/dL vs. ≥ 10g/dL)
- Baseline creatinine clearance (CrCL) (< 30, 30 - < 60, ≥ 60 ml/min)
  The creatinine clearance will be calculated using Cockroft-Gault formula, defined as:

Formula 1 (for males):

$$CrCL(ml/min) = \frac{(140 - age(in\ years)) * weight(in\ kg)}{72 * serum\ creatinine(in\ mg/dL)}$$

or Formula 2 (for females):

$$CrCL(ml/min) = \frac{(140 - age(in\ years)) * weight(in\ kg)}{72 * serum\ creatinine(in\ mg/dL)} * 0.85$$

  Baseline weight will be used.
- Time from Initial Disease Diagnosis to Assignment (<1 year, , ≥2 years)

- Platinum resistant/refractory versus platinum sensitive based on the prior systemic cancer therapy
- Smoking status

7.3.3 Medical History

General medical history will be listed by subject.

7.3.4 Prior Therapy

The following will be summarized for the expansion cohort (nivolumab and nivolumab 1 mg/kg + Ipilimumab 3 mg/kg treatment groups):

- Prior neo-adjuvant therapy (yes/no)
- Prior adjuvant therapy (yes/no)
- Time from completion of prior adjuvant therapy to assignment (subjects who received prior adjuvant therapy), (< 6 months and ≥ 6 months)
- Prior surgery related to cancer (yes/no)
- Prior radiotherapy (yes/no)
- Number of prior therapies received (1, 2, 3, ≥4)
- Best response to most recent prior regimen (CR/PR vs SD vs PD)
- Time from first line treatment to start of second line treatment (≤ 90 days and > 90 days)
- Prior platinum experience (cisplatin only, carboplatin only, both or other) by setting
- Time from completion of most recent prior regimen to study treatment (< 3, 3- < 6, ≥ 6 months)

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 for the expansion cohort (nivolumab and nivolumab 1 mg/kg + ipilimumab 3 mg/kg treatment groups). A by-subject listing will accompany the table.

7.4 Extent of Exposure

Analyses in this section will be performed for the expansion cohort (nivolumab and nivolumab 1 mg/kg + ipilimumab 3 mg/kg treatment groups).

For the analyses of crossover subjects during original assigned treatments, the exposure will be truncated at the first crossover dose date. All others will follow regular counting rules.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by treatment group (refer to Table 7.4.1-1):

- Relative dose intensity (%) using the following categories: <50%, 50 - <70%; 70 - <90%; 90 - <110%; ≥110%
- Number of doses of nivolumab, ipilimumab (summary statistics)
- Duration of treatment: duration of treatment will be presented 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 extent of exposure (weight, number of doses, date of first and last dose, cumulative dose, relative dose intensity, duration of treatment, and reason for discontinuation) and a listing of batch number will be provided.

Table 7.4.1-1: Study Therapy Parameter Definitions

	Nivolumab in Arm N	Nivolumab in Arm N-I Dose Levels 1, 2 and 2b	Ipilimumab in Arm N-I Dose Levels 1, 2, and 2b
Dosing Schedule per Protocol	2 mg/kg every 2 weeks	1 or 3 mg/kg every 3 weeks for 4 doses followed by 3 mg/kg every 2 weeks OR Maximum tolerable dose identified in escalation phase.	1 or 3 mg/kg every 3 weeks for 4 doses
Dose	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL)*total volume infused (mL)]/most recent weight (kg) and nominal dose (mg/kg)*total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL)*total volume infused (mL)]/most recent weight (kg) and nominal dose (mg/kg)*total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL)*total volume infused (mL)]/most recent weight (kg) and nominal dose (mg/kg)*total volume infused (mL) /total volume prepared (mL)
Cumulative Dose	Cum Dose (mg/kg) is the sum of the doses administered to a subjects.	Cum Dose (mg/kg) is the sum of the doses administered to a subjects.	Cum Dose (mg/kg) is the sum of the doses administered to a subjects.
Dose Intensity (%)	7x Cum dose/(Last dose date - Start dose date + 14)	For Combo phase (the first two cycles): 7x Cum dose in Combo phase /(Last dose date in Combo phase - Start dose date + 21) For Mono phase (cycle 3 and beyond): 7x Cum dose in Mono phase /(Last dose date - Start dose date in Mono phase + 14)	7x Cum dose/(Last dose date - Start dose date + 21)
Relative Dose Intensity (%)	Cum dose /[(Last dose date - Start dose date + 14) x 3/14] x 100	Cum dose/[(3 or 1) x (Last dose date - Start dose date + 21)/21] x 100, if the last dose is in Combo phase Cum dose/[(3 or 1) x 4 + 3 x (Last dose date - 84 + 14)/14] x 100, if the last dose is in Mono phase	Cum dose/[(3 or 1) x (Last dose date - Start dose date + 21)/21] x 100, if subjects don't have re-exposure. Cum dose/[(3 or 1) x (Last dose date - Gap - Start dose date + 21)/21] x 100, where Gap is between stop date and re-exposure date for subjects with re-exposure.
Duration of Treatment	*Last dose date - Start dose date + 1*	*Last dose date - Start dose date + 1*	*Last dose date - Start dose date + 1*

Volume infused, volume prepared, and weight are collected on the CRF. Nominal nivolumab dose collected in IVRS. i = 1, 2,...,N, where N = number of infusions. Cycle Duration (N) = 3 weeks for nominal 1 or 3 mg/kg nivolumab doses and 2 weeks for nominal 3

mg/kg. Intended dose per week is .33 or 1 mg/kg for nominal 1 or 3 mg/kg nivolumab doses and 1.5 mg/kg nivolumab doses. If different from the above dosing, the MTD will be used for ARM N-I.

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 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 dose delays per subject, length of delay (4 - <8 days, 8 - <15 days, 15- <42 days, ≥42 days), and reason for delay.

7.4.2.2 Infusion Interruptions and Rate Changes

Each nivolumab or ipilimumab infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

The following parameters will be summarized by treatment group:

- Number of subjects with at least one dose infusion interruption, the reason for interruption, and the number of infusion interruptions per subject.
- Number of subjects with at least one IV infusion rate reduction and the reason for reduction.

7.4.2.3 Dose Escalations

Dose escalations are not permitted for either nivolumab or ipilimumab.

7.4.2.4 Dose Reductions

Dose reductions are not permitted for either nivolumab or ipilimumab.

7.4.2.5 Dose Omissions

Dose omissions are not permitted for either nivolumab or ipilimumab.

[redacted]

7.5 Efficacy

The efficacy analyses will be performed on the SCLC expansion cohort (nivolumab and nivolumab 1 mg/kg + ipilimumab 3 mg/kg treatment groups).

7.5.1 Objective Response Rate

7.5.1.1 Analysis for Primary Objective of SCLC Expansion Cohort

The primary objective for the SCLC expansion cohort is to compare the ORR as assessed by BICR for nivolumab monotherapy versus nivolumab combined with ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg). This primary objective will be assessed when all subjects have been assigned/treated for approximately 6 months.

The comparison of ORR as per BICR assessment will be conducted using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by the stratification factor as per IVRS [number of prior treatment lines (1 vs. 2 prior chemotherapy regimens)]. An associated odds ratio and 95% CI will also be computed. An estimate of the difference in ORRs and corresponding CI will be calculated using CMH methodology and stratified by the stratification factor per IVRS (number of prior treatment lines). The number and percentage of subjects in each category of best overall response as assessed by BICR per RECIST v1.1 criteria (complete response, partial response, stable disease, progressive disease, or unable to determine) will be presented by treatment group. An estimate of the response rate and an associated exact two-sided 95% CI using Clopper and Pearson method will be presented by treatment group.

Similar methods will be used to summarize ORR for each stratification factor [number of prior treatment lines (1 vs. 2 prior chemotherapy regimens)]. However, the p-value will not be provided for each stratification factor.

DOR as determined by the investigator or BICR will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using the log-log transformation will also be calculated by treatment group. In addition, the percentage of responders still in response at different time points (3, 6, 12, 18, and 24 months) will be presented based on the KM plot.

To summarize the magnitude of reduction in tumor burden, a waterfall plot of best percentage reduction from baseline in sum of diameters of target lesions will be generated.

7.5.1.2 Sensitivity Analysis

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

- Best unconfirmed overall response
- Best confirmed overall response where all response designations contribute to the BOR determination, regardless of start of subsequent therapy/crossover
- Best unconfirmed overall response where all response designations contribute to the BOR determination, regardless of start of subsequent therapy/crossover.

Sensitivity analyses of DOR will also be performed using the following modification:

- DOR accounting for assessment on/after subsequent therapy/crossover. DOR will be defined similarly to the primary analysis, but regardless of start of subsequent therapy/crossover.

7.5.2 Progression Free Survival

7.5.2.1 Primary Analysis

PFS is determined by the investigator or BICR. The PFS curves for each treatment group of the SCLC expansion cohort will be estimated using the KM product-limit method. Two-sided 95% CIs for median PFS will be computed using the log-log transformation.

PFS rates at 3, 6, 12, 18, and 24 months will be estimated using KM estimates on the PFS curve for each treatment arm of the SCLC expansion cohort. Minimum follow-up must be longer than the timepoint to generate the rate. The associated two-sided 95% CI will also be calculated. Additional survival analysis may be conducted for up to 5 years beyond analysis of the primary endpoint.

The source of progression (death vs. progression) will be summarized.

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

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

7.5.2.2 Sensitivity Analysis

Sensitivity analyses of PFS will also be performed using the following modification:

- PFS accounting for assessment on/after subsequent therapy. PFS will be defined similarly to the primary analysis except that events (progression or death) and tumor assessments that occurred on or after subsequent anti-cancer therapy will be taken into account.

7.5.3 Overall Survival

OS curves for each treatment arm in the SCLC expansion cohort will be estimated using the KM product limit method. Median OS and the corresponding two-sided 95% CIs using the log-log transformation will be computed. Survival rates at 3, 6, 12, 18, and 24 months will be estimated using KM estimates on the OS curve for each treatment arm in the expansion cohort. Minimum follow-up must be longer than the timepoint to generate the rate. Associated two-sided 95% CIs will be calculated. Additional survival analysis may be conducted for up to 5 years beyond analysis of the primary endpoint.

For crossover subjects, no data will be truncated.

7.5.3.1 Subject Follow-up

The extent of follow-up defined as the time between assignment 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 assigned subjects.

The currentness of follow-up, 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 for the SCLC expansion cohort. Subjects who died and subjects with a Last Known Date Alive on or after LPLV will have a value of '0' for currentness of follow-up. The currentness of follow-up will be categorized into the following categories: 0 days, >0 to <3 months, ≥3 to 6 months, ≥6-9 months, ≥9-12 months, ≥12-15 months, or ≥ 15 months.

7.5.3.2 Subsequent Therapy

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

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

A by-subject listing of follow-up therapy will be produced for subjects who had any subsequent therapy.

7.6 Safety

For all safety related analyses, refer to the Core Safety SAP[11]. As noted in Section 7.1, safety will be summarized for all treated subjects in the SCLC pooled pre-expansion and expansion cohorts, by treatment group (Nivolumab and Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg).

In addition, the following select safety summaries will be summarized for all subjects in the SCLC expansion cohort, by treatment group (Nivolumab and Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg):

- Summary of Drug-Related Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
- Summary of Drug-Related Serious Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)

- Summary of Drug-Related Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
- Death Summary

For the analyses of crossover subjects during original assigned treatments, all the AE will be truncated at the first crossover dose date. All others will follow regular counting rules. For the analysis of crossover subjects during crossover period, all the AE will be counted at the first crossover dose date.

Treatment-related AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. All on-study AEs, Grade 3-4 AEs, treatment-related AEs, Grade 3-4 treatment-related AEs, SAEs, treatment-related SAEs, and AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function and Grade 3-4 Lab Abnormalities will be summarized using grade NCI CTCAE v 4.0 criteria.

7.6.1 Deaths

See Core Safety SAP.

7.6.2 Serious Adverse Events

See Core Safety SAP.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP.

7.6.4 Adverse Events Leading to Dose Delay of Study Therapy

See Core Safety SAP.

7.6.5 Adverse Events

See Core Safety SAP.

7.6.6 Select Adverse Events

See Core Safety SAP.

7.6.7 Immune Modulating Medication

See Core Safety SAP.

7.6.8 Multiple Events

See Core Safety SAP.

7.6.9 Clinical Laboratory Evaluations

7.6.9.1 Hematology

See Core Safety SAP.

7.6.9.2 Serum Chemistry

See Core Safety SAP.

7.6.10 Immunogenicity

See Core Safety SAP.

7.6.11 Vital Signs and Pulse Oximetry

See Core Safety SAP.

7.7 Pregnancy

See Core Safety SAP.

7.8 Pharmacokinetics

Summary statistics will be calculated for nivolumab and ipilimumab concentrations, and summarized by scheduled sample collection time. The nivolumab concentration 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. In addition, exposure-response analyses with selected efficacy and safety endpoints will be conducted. Results of population PK and exposure-response analyses will be reported separately.

[redacted]

[redacted]

medium, high)

[redacted]

CI for median OS in each treatment group will be computed via the log-log transformation [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[12]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[13].

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 day and the maximum will be considered as the death date.
- If the month of the year is missing, the death date will be imputed as the last known date alive day.
- 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 day.

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

*In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions may be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

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

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

Duration = (Last date - first date + 1)

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

9 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.