Official Title of Study:

AN OPEN-LABEL, RANDOMIZED, PHASE 3 STUDY OF NIVOLUMAB OR

CHEMOTHERAPY IN SUBJECTS WITH RELAPSED SMALL-CELL LUNG CANCER

AFTER PLATINUM-BASED FIRST LINE CHEMOTHERAPY (CHECKMATE 331:

CHECKPOINT PATHWAY AND NIVOLUMAB CLINICAL TRIAL EVALUATION 331)

NCT Number: NCT02481830

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

AN OPEN-LABEL, RANDOMIZED, PHASE 3 STUDY OF NIVOLUMAB OR CHEMOTHERAPY IN SUBJECTS WITH RELAPSED SMALL-CELL LUNG CANCER AFTER PLATINUM-BASED FIRST LINE CHEMOTHERAPY (CHECKMATE 331: CHECKPOINT PATHWAY AND NIVOLUMAB CLINICAL TRIAL EVALUATION 331)

PROTOCOL CA209-331

VERSION # 2.0

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[REDACTED]

Research Hypothesis:

Treatment with nivolumab will increase OS as compared with chemotherapy in subjects with relapsed SCLC treated with prior platinum-based, first-line chemotherapy.

Schedule of Analyses:

The final analysis will take place 34 months after first patient was randomized and no formal interim analysis will be conducted. The 560 subjects (including at least 78 subjects randomized in China) are expected to be randomized in 18 months, resulting in about 16 months of follow-up for the last subject randomized at the time of the primary analysis. It is anticipated that approximately 482 events will be observed at the time of the analysis (see Section 5 for details).

2 STUDY DESCRIPTION

2.1 Study Design

This is a randomized, open-label, two-arm, multicenter, Phase 3 study in adult subjects with relapsed SCLC treated with prior platinum-based, first-line chemotherapy. Subjects must have had at least 4 cycles of platinum-based, first-line chemotherapy, or if they received less than 4 cycles, they must have had a best overall response (BOR) of a partial or complete response after completion of chemotherapy.

Approximately 480 subjects will be randomized in a 1:1 ratio to treatment with either nivolumab (Arm A) or chemotherapy (either topotecan or amrubicin, Arm B) in the Global Population. In addition, this study includes a cohort of at least 78 additional randomized patients from China (~16% of the global number of randomized subjects). The primary population for safety and efficacy analysis will include subjects from the Global Population as well as subjects from the additional Chinese cohort, leading to a total sample size of about 560 subjects.

Subjects will be stratified according to the following factors:

- Response to first-line platinum based treatment: platinum sensitive (progression-free interval ≥ 90 days after completion of platinum therapy) vs platinum resistant (progression-free interval < 90 days after completion of platinum therapy)
- Brain metastases at baseline: yes vs. no.

On-study tumor assessments will begin at Week 6 post randomization (± 5 days) and be performed every 6 weeks (± 5 days) until Week 30. After Week 30, tumor assessments will be performed every 12 weeks (± 5 days) until disease progression (or until discontinuation of study drug in subjects receiving nivolumab beyond investigator-assessed progression) lost to follow-up, withdrawal of study consent, or the study ends.

Enrollment will end after approximately 560 subjects have been randomized (including ~78 additional subjects in China).

The primary endpoint of the study is OS.

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

Accrual duration is expected to be approximately 18 months; overall study duration will be approximately 34 months (18 months accrual + minimum follow up of 16 months). The study will end when analysis of survival is complete. Additional survival follow-up may continue for up to 5 years from the time of this analysis.

A DMC will be utilized to provide general oversight and safety considerations for this study, CA209331.

Figure 2.1-1:   **Study Schematic**
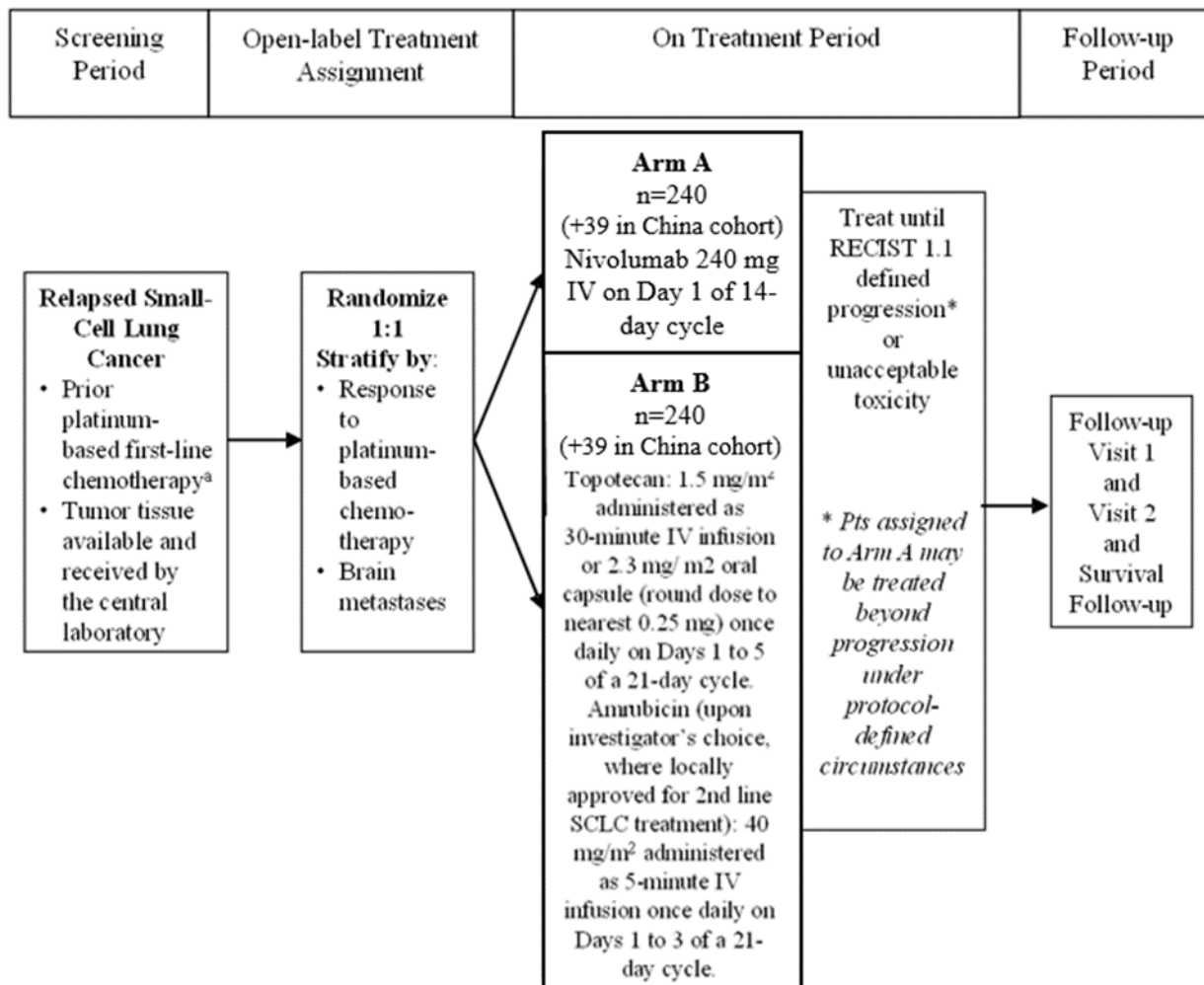
a   Subjects must have had at least 4 cycles of platinum-based, first-line chemotherapy, or if they received less than 4 cycles of platinum-based first-line chemotherapy, they must have had a best overall response (BOR) of at least a partial or complete response after completion of chemotherapy.

2.2   Treatment Assignment

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

- Date of birth
- Date of informed consent
- Gender.
- Subject number

- Confirmation that all randomization inclusion/exclusion are met
- Confirmation that FFPE tumor tissue block or unstained slides were received by the central laboratory
- Response to first-line platinum-based treatment: platinum sensitive vs platinum resistant
- Brain metastases at baseline: yes vs. no.

If the above are met, the IVRS will randomly assign subjects to treatment Arm A or Arm B in a 1:1 ratio using a stratified permuted block randomization method with respect to the following stratification factors:

- Response to first-line platinum based treatment: platinum sensitive vs platinum resistant
- Brain metastases at baseline: yes vs. no.

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

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

Table 2.4-1: **Protocol Amendment**

Document	Date of Issue	Summary of Change
Revised Protocol 03	15-Mar-2018	Incorporates Amendment 17 and Administrative Letters 04, 05 and 06
Amendment 17	15-Mar-2018	- Updated study personnel - Added additional China cohorts in Arm A and Arm B ████████████████████████ - Updated protocol as per nivolumab program standards
Administrative Letter 06	19-Dec-2017	Change in Medical Monitor contact
Administrative Letter 05	06-Dec-2017	Change in Medical Monitor contact
Administrative Letter 04	29-Jun-2017	Change in Medical Monitor contact
Revised Protocol 02	07-Sep-2016	Incorporates Amendment(s) 15 and Administrative Letter 03
Amendment 15	07-Sep-2016	Remove the planned interim analysis and to modify the timing of the final analysis as a result from a phase 1/2 study (CheckMate 032) which suggested a treatment delayed effect for immunotherapy in Small Cell Lung Cancer. The amendment will also add a sub-study in China to comply with regulatory requirement in that country ████████████████████████

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Table 2.4-1: **Protocol Amendment**

Document	Date of Issue	Summary of Change
		on results of Checkmate 017 and Checkmate 057
		Other changes include correction of inconsistencies, alignment with latest Nivolumab standards, and investigator brochure.
Administrative Letter 03	05-Feb-2016	Edited misleading/ambiguous sentence about the contraception method to be used.
Revised Protocol 01	15-Dec-2015	Incorporates Amendment(s) 11 and Administrative Letters 01 & 02
Amendment 11	15-Dec-2015	The main purpose of this amendment is to allow the use of different topotecan formulations (powder for injection and oral capsules). Other changes include modification of the treatment assignment for Arm B to allow for treatment with topotecan or amrubicin (upon investigator's choice, where locally approved for 2nd line SCLC patients), clarification of some inclusion/exclusion criteria, correction of inconsistencies and typographical revisions throughout the protocol. Change of Medical Monitor
Administrative Letter 02	08-Dec-2015	Change of Study Director and Medical Monitor
Administrative Letter 01	14-Jun-2015	Criterion deleted given because not applicable to the approved original protocol
Original Protocol	22April2015	Not applicable

2.5   Data Monitoring Committee

An independent Data Monitoring Committee (DMC)will be utilized. The DMC will be utilized to provide general oversight and safety considerations for this study, CA209331. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety data for the study. The DMC will be advisory to the clinical study leadership team. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required. Details of the DMC responsibilities and procedures will be specified in the DMC charter.

In addition, the Sponsor will independently review safety data in a blinded manner during the conduct of this trial to ensure that any safety issues are identified and addressed.

3 OBJECTIVES

3.1 Primary

To compare the OS of nivolumab versus chemotherapy in subjects with relapsed SCLC after platinum-based, first-line chemotherapy.

3.2 Secondary

Secondary objectives are:

- To compare the PFS of nivolumab versus chemotherapy
- To compare the ORR of nivolumab versus chemotherapy.

4   ENDPOINTS

4.1   Primary Endpoints

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

4.2   Secondary Endpoints

4.2.1   Progression - Free Survival

Progression-free survival (PFS) is defined as the time from randomization to the date of the first documented tumor progression as determined by the investigator using RECIST 1.1 criteria or death due to any cause. Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) is not considered progression for purposes of determining PFS. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any baseline or on-study tumor assessments and did not die will be censored on the date they were randomized. Subjects who received any subsequent anti-cancer therapy (including on-treatment palliative RT of non-target bone lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

Table 4.2.1-1:   **Censoring Scheme for Primary Definition of PFS**

```
                          BASELINE
                            SCAN
                         AVAILABLE?
            ┌───────────────────┴────────────────┐
                                                Yes
   No: Censored at                                │
   rand (regardless of                   ON-STUDY SCANS
   death)                                   AVAILABLE?
                          ┌────────────────────┴─────────────────────┐
                         No                                         Yes
                          │                        ┌──────────────────┴──────────────┐
                       DEATH?                 NO PD, NO DEATH            PD OR DEATH OR BOTH
            ┌─────────────┴──────────┐             │                            │
          Yes                        │       Started Subsequent     Subsequent Therapy <
                            No: Censored            Therapy?          PD or death or min (PD,
                              at rand                                        death)?
         Death without prior             Yes: Censored at max        Yes: Censored at max
      ─Subsequent Therapy:               ( rand, last tumor        ─(rand, last tumor scan <=
         Event at Death date             scan <= Subseq Ther         Subseq Ther date)
                                         date)
         Death with prior               No: Censored at last        No: Event at PD or
      ─Subsequent Therapy:              tumor scan date           ─death or min (PD, death
         Censored at rand                                            date)
```

4.2.2   *Objective Response Rate*

Objective response rate (ORR) is defined as the number of subjects whose best objective response (BOR) is a confirmed CR or confirmed PR, as determined by the investigator, divided by the number of randomized subjects. BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent anticancer therapy (excluding on-treatment palliative radiotherapy), whichever occurs first. For subjects without documented progression or subsequent anticancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue treatment beyond progression, the BOR will be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

4.2.3   Duration of Objective Response

DOR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), as determined by the investigator, or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the duration of objective response will be censored on the date of their last evaluable tumor assessment. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. DOR will be evaluated for confirmed responders (i.e. subjects with confirmed CR or PR) only.

Duration of Stable Disease will also be evaluated for subjects with SD as best response. Duration of SD is defined as the time between the randomization date to the date of the first documented tumor progression (per RECIST 1.1), as assessed by the investigator, or death due to any cause, whichever occurs first. Censoring rules will be the same as for DOR analysis.

4.2.4   Time to Objective Response

Time to Objective Response (TTR) is defined as the time from randomization to the date of the first confirmed response. TTR will be evaluated for confirmed responders only.

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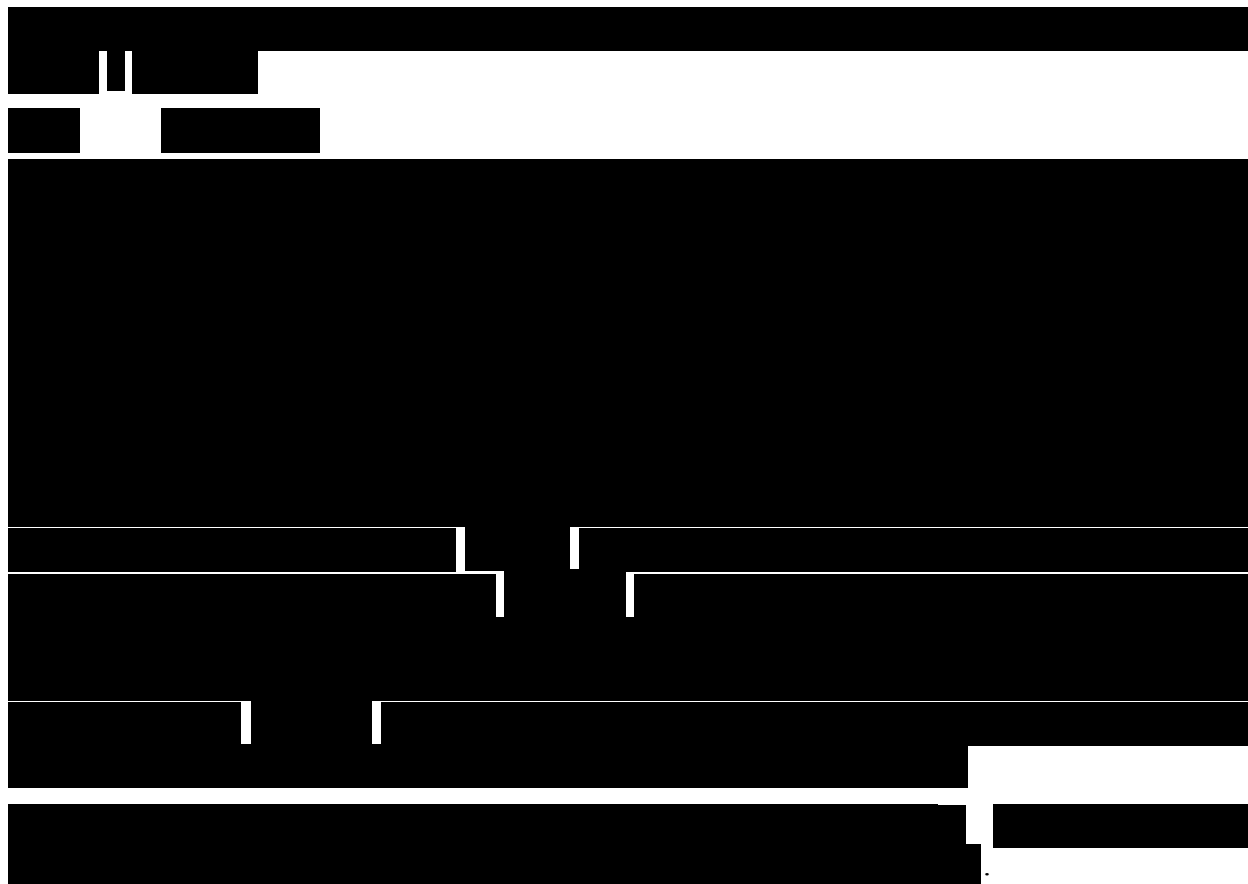
5   SAMPLE SIZE AND POWER

Results of a Phase 1/2 study of nivolumab, with or without ipilimumab, for treatment of recurrent SCLC (CA209032)[5] seem to suggest a delayed treatment effect for immunotherapy in SCLC. Statistical assumptions for CA209331 have been updated accordingly, based on the median OS observed in subjects treated with nivolumab after failing first-line chemotherapy in CA209032. This delayed effect would be consistent–with what has been observed in other published trials comparing nivolumab to chemotherapy in other solid tumor types.[6,7]

In this study, the primary endpoint of OS will be evaluated for treatment effect at the overall alpha level of 0.05 (two-sided). Approximately 560 subjects will be randomized at a ratio of 1:1 into
two arms: Arm A (nivolumab); Arm B (chemotherapy: topotecan or amrubicin). For sample size calculation, non-proportional hazard model with a piecewise exponential distributions in both arms are assumed. Based on published survival curves for topotecan, a 2-piece exponential distribution with an 8-month median OS and taking into account that a limited number of subjects might receive immuno-oncology as subsequent therapy, a conservative 5% 2-year survival rate is assumed for the control arm. A delayed effect for nivolumab with a hazard ratio (HR) of 1 for the first 8 months and an HR of 0.5 thereafter is assumed. The final analysis will take place 34 months after the first patient have been randomized and no formal interim analysis will be conducted. The 560 subjects are expected to be randomized in 18 months, resulting in

about 16 months of follow-up for the last subject randomized at the time of the primary analysis. It is anticipated that approximately 480 events will be observed at the time of the analysis, leading to 90% power to detect a difference in overall survival as tested via a log-rank test with a two-sided 0.05 type I error rate. Power calculations were performed using EAST® Software (Version 6.4.1).The decision to incorporate the China subset into the overall population for analysis is the result of a review of the protocol statistical assumptions in comparison to recent data from the CA209032 study in 2L+ SCLC subjects[8]. The data from CA209032, which were not available at the time of protocol design, suggest a delayed effect of nivolumab with a non-proportional hazard for survival. Additionally, review of recently generated real-world data for topotecan resulted in updated assumptions for the control arm. Given the updated statistical assumptions, incorporation of the China subset into the study analyses grants adequate statistical power by increasing the study sample size.

Table 5-1:   **Sample Size Justification**

Primary Endpoint	OS
Power	90%
Alpha level	0.05
Sample size	560
Accrual duration	18 months
Timing of the analysis from randomization of first subject (months)	34
Hypothesized OS rate at 8 months	50% in both arms (HR=1 up to Month 8)
Hypothesized OS rate at 24 months	5% vs. 16% (HR=0.5 from Month 8)
Expected Average HR	~0.745
Expected number of event at 34 months	482

The secondary endpoints PFS and ORR will be tested hierarchically (see Section 7.5.6).

6   STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1   Study Periods

See Core Safety SAP.

6.2   Treatment Regimens

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

- Arm A: Experimental Arm (monotherapy) nivolumab
- Arm B: Control arm Topotecan/amrubicin (investigator's choice)

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

6.3 Populations for Analyses

- **All enrolled subjects**: All subjects who sign an informed consent form and are registered into the IVRS

- **All randomized subjects**: All enrolled subjects who are randomized to any treatment arm in the study. This is the primary dataset for analyses of efficacy and baseline characteristics.

- **All treated subjects**: All enrolled subjects who received at least one dose of nivolumab, or chemotherapy. This is the primary dataset for dosing and safety.

- **PK subjec**ts: All enrolled subjects with available serum time-concentration data from randomized subjects dosed with nivolumab.

- **Tumor Mutational Burden** (TMB) evaluable Subjects: All randomized subjects with baseline evaluable TMB

- ███.

- **China Cohor**t: all subjects enrolled in China. Additional analyses exploring the consistency of findings in the China cohort may be conducted. Details of these analyses will be provided in the analysis plan.

7 STATISTICAL ANALYSES

7.1 General Methods

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

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

Median survival time along with 95% CI will be constructed based on Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals)[9,10]. Rates at fixed timepoints (e.g. OS at 6 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula[11] for variance derivation and on log-log transformation applied on the survivor function $S(t)$[12].

Unless otherwise specified, the stratified log-rank test will be performed to test the comparison between time to event distributions (OS and PFS). Stratification factors will be Response to first-line platinum based treatment: platinum sensitive vs. platinum resistant, and Brain metastases at baseline: yes vs no, as entered into the IVRS.

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

The difference in rates between the two treatment arms along with their two-sided 95% CI will be estimated using the following Cochran-Mantel-Haenszel (CMH) method of weighting[13], adjusting for the stratification factors:

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

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

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

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

7.2   Study Conduct

7.2.1   Accrual

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

7.2.2   Relevant Protocol Deviations

The relevant Protocol Deviations will be summarized for all randomized subjects, by treatment group and overall. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

At entrance:

- Subjects without confirmed SCLC.
- Subject with baseline ECOG PS > 1.
- Subjects without evaluable disease at baseline.
- Subjects who received prior treatment with topotecan or amrubicin,

- Subjects who received less than 4 cycles of platinum-based, first-line chemotherapy without a best overall response (BOR) of a partial or complete response after completion of chemotherapy

On-Study:

- Subjects receiving concurrent anti-cancer therapy (defined as chemotherapy, hormonal immunotherapy, radiation therapy, standard or investigational agents for treatment of SCLC).
- Subject treated differently as randomized (subjects who received the wrong treatment, excluding the never treated).

A subject listing will also be produced.

7.3   Study Population

7.3.1   Subject Disposition

The total number of subjects enrolled (randomized or not randomized) will be presented along with the reason for not being randomized.

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

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

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

7.3.2   Demographics and Other Baseline Characteristics

The following baseline characteristics will be summarized by treatment arm as randomized. All baseline presentations identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics).
- Age category (< 65, $\geq 65 - < 75$, ≥ 75, ≥ 65).
- Gender, Race/Ethnicity, Region (US/Canada vs. Europe vs. Asia vs. Rest of World).
- Baseline ECOG PS,
- Baseline Weight (kg).
- Baseline LDH ($\leq$ ULN, $>$ ULN)
- Baseline LDH ($\leq$ 2x ULN, $>$ 2x ULN)
- CNS Metastasis (Yes/no)

- Cell type: (SCLC; other)
- Smoking Status (current/former; never smoked; unknown)
- Disease stage: Extensive versus Limited subjects (Source: eCRF)
- 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 diameters of target lesions.

7.3.3   Medical History

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

7.3.4   Prior Therapy Agent

Prior therapy will be summarized in a single table (Source: CRF).

Prior anti-cancer therapy.

- Line of therapy (First/Unknown)
- Number of cycle of Platinum first line therapy
- Number of cycle of Etoposide as first line therapy
- Number of cycle of Irinotecan as first line therapy
- Best response to 1st line (CR/PR vs. SD vs. PD).
- Primary reason for discontinuation of 1st line therapy
- Time from completion of most recent regimen to treatment (< 3, 3 - 6, > 6 months).
- Prior surgery related to cancer (yes or no).
- Prior PCI (yes or no).
- Prior radiotherapy (yes/no)
- Prior systemic therapy classified by therapeutic class and generic name.

Other Prior therapy:
- Prior/current non-study medication classified by anatomic and therapeutic classes.

Agents and medication will be reported using the generic name. A listing by subject will also be provided.

7.3.5   Baseline Examinations

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

7.3.6 Discrepancies between IVRS and CRF Stratification Factors

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

7.4 Extent of Exposure

7.4.1 Administration of Study Therapy

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

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

Duration of treatment will be presented by treatment group using a Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off study therapy. Median duration of treatment and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date.

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

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

Table 7.4.1-1:   Administration of study therapy: definition of parameters

	Nivolumab	Topotecan IV	Topotecan Oral	Amrubicin
Dosing schedule per protocol	240mg every 2 weeks	1.5mg/m² for days 1 to 5 of every 3 weeks cycle	2.3mg/m² for days 1 to 5 of every 3 weeks cycle	40mg/m² for days 1 to 3 of every 3 weeks cycle
Dose	*Dose* is defined as Total Dose administered (mg)	*Dose (mg/m²)* is defined as Total Dose administered (mg) / Most recent BSA. Dose administered in mg at each dosing date and BSA (computed using recent weight and bsl height) are collected on the CRF.	*Dose (mg/m²)* is defined as Total Dose administered (mg) / Most recent BSA. Dose administered in mg at each dosing date and BSA (computed using recent weight and bsl height) are collected on the CRF.	*Dose (mg/m²)* is defined as Total Dose administered (mg) / Most recent BSA. Dose administered in mg at each dosing date and BSA (computed using recent weight and bsl height) are collected on the CRF.
Cumulative Dose	*Cum dose is* sum of the doses (mg) administered to a subject during the treatment period.	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject during the treatment period.	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject during the treatment period.	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject during the treatment period.
Relative dose intensity (%)	Cum dose (mg) / [(Last dose date - Start dose date + 14) x 240 / 14] x	Cum dose (mg/m²) / [(First dose date in last cycle - Start dose date	Cum dose (mg/m²) / [(First dose date in last cycle - Start dose	Cum dose (mg/m²) / [(First dose date in last cycle - Start dose

21

Table 7.4.1-1: **Administration of study therapy: definition of parameters**

	Nivolumab	Topotecan IV	Topotecan Oral	Amrubicin
	100	+ 21] x 7.5 / 21] x 100	date + 21) x 11.5 / 21] x 100	date + 21) x 120 / 21] 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	Last dose date - Start dose date +1

7.4.2 Modifications of Study Therapy

7.4.2.1 Cycle Delays

A cycle 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 topotecan/amrubicin. It is defined as (duration of previous cycle in days -14) for nivolumab (or -21 for topotecan/amrubicin). Cycle delays will be divided into following categories: on-time, 4 - 7 days, 8 - 14 days, 15 - 42, > 42 days. Reason for Cycle delay will be retrieved from CRF dosing pages.

Each nivolumab or topotecan/amrubicin 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 arm:

- Number of cycle delayed per subject, Length of Delay and Reason for cycle Delay.
- Number of subject with at least one dose infusion interrupted along with reason for the interruptions and number of infusions interrupted per subject.

7.4.2.2 Topotecan/Amrubicin Dose interruptions - IV

Topotecan/amrubicin dose interruption will occur if, on Day 1 to Day 5 of each cycle for topotecan or on Day 1 to Day 3 of each cycle for amrubicin, the subject had an IV infusion interruption. Reason for dose interruption will be retrieved from CRF dosing pages.

7.4.2.3 Dose Reductions/Omissions/Increases

There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days from the previous dose.

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

Dose of topotecan/amrubicin may be modified for toxicity. Subjects may be dosed no less than 14 days from the previous dose. Based on local guideline, providing subjects is not experiencing significant toxicity, increase topotecan IV dosage to a maximum of 2mg/m² per day (3.1mg/m² per day for the oral formulation) in increments of 0.25mg/m² per day (0.4mg/m² per day for oral formulation) is possible.

Per the Protocol, dose levels of topotecan IV are defined as:

- Dose level +2: 2mg/m²
- Dose level +1: 1.75mg/m²
- Dose level 0: 1.5mg/m²
- Dose level -1: 1.25mg/m²
- Dose level -2: 1mg/m²

Per the Protocol, dose levels of Oral topotecan are defined as:

- Dose level +2: 3.1mg/m²
- Dose level +1: 2.7mg/m²
- Dose level 0: 2.3mg/m²
- Dose level -1: 1.9mg/m²
- Dose level -2: 1.5mg/m²

Per Protocol, dose levels of amrubicin are defined as follow:

- Dose level 0: 40mg/m²
- Dose level -1: 35 mg/m²
- Dose level -2: 30mg/m²
- Dose level -3: 25mg/m²

Dose reduction/increase, on Day 1 to Day 5 of each cycle for topotecan or on Day 1 to Day 3 of each cycle for amrubicin, is defined as at least one day with a non zero dose smaller/higher than 1mg/m² for topotecan IV (1.5mg.m² for Topotecan oral and 40mg/m² for amrubicin) and smaller than previous non zero dose (with a CRF reason different from "Dosing Error" for oral topotecan).

Dose Omission: a dose is considered as being omitted during a cycle when less than 5 or less than 3 non zero doses have been reported for Topotecan (unless, for oral topotecan, CRF reason is "Dosing Error") and for amrubicin, respectively.

Dose ranges for dose levels of Topotecan and amrubicin are defined in Table below

Table 7.4.2.3-1:   Dose Modifications

Dose Range (mg/m^2)			Dose Level
Topotecan IV	**Topotecan Oral**	**Amrubicin**	
≥ 1.825	≥ 2.9	NA	Level +2
1.625 – < 1.825	2.5 – <2.9	NA	Level +1
1.375 – < 1.625	2.1 - <2.5	≥ 37.5	Level 0
1.125 – < 1.375	1.7 - <2.1	32.5 – < 37.5	Level -1

Table 7.4.2.3-1: **Dose Modifications**

Dose Range (mg/m^2)			Dose Level
Topotecan IV	**Topotecan Oral**	**Amrubicin**	
< 1.125	1.3 - <1.7	27.5 – < 32.5	Level -2
NA	NA	< 27.5	Level -3

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

For Nivolumab and Topotecan, the following will be summarized by treatment group:

- Number of subjects with at least one infusion with IV rate reduced along with the reason of the rate reduction.

The following will be summarized for topotecan and amrubicin subjects:

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

- Number and percentage of subjects with at least one dose increase of topotecan, number and percentage of subjects with a dose increase to dose level +1, number and percentage of subjects with a dose reduction to dose level

A by-subject listing will accompany the table.

7.5 Efficacy

7.5.1 Overall Survival

7.5.1.1 Primary Analysis

The distribution of OS will be compared in two randomized arms at the interim and final analyses via a two-sided, log-rank test stratified by baseline stratification factors, as entered into the IVRS.

The hazard ratio (HR) and the corresponding $100(1-\alpha)\%$ CI (adjusted for the interim) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate.

The OS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be constructed based on a log-log transformed CI for the survivor function S(t) [10].

Based on the availability of the data, survival rates at 6, 12, 18, 24, 36, 48 months and at 5 year will also be estimated using KM estimates on the OS curve for each randomized arm. Minimum follow-up must be longer than timepoint to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood's formula[11] for variance derivation and on log-log transformation applied on the survivor function S(t)

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

- on-study (on-treatment and not progressed, on-treatment progressed, in follow-up);
- off-study: (lost to follow-up, withdraw consent, etc.).

Unless otherwise specified, the primary population will be the all randomized population.

7.5.1.2 OS Sensitivity Analyses

Non-Proportional Hazard Assumption

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

In case non-proportionality cannot be ruled out by the test described above, piecewise hazard ratios (e.g. from 0 to 8 months and after 8months) will be presented together with their corresponding 95% CI.

To investigate the impact of potential non-proportional hazard, the distribution of OS will also be compared using a two-sided weighted log-rank test stratified by the stratification factors, as entered into the IVRS. The weighted log-rank test will use G (rho = 0, gamma = 1) weights, in the terminology of Fleming and Harrington[14],[15]. This p-value will be considered as descriptive.

Additional Sensitivity Analyses

The following OS sensitivity analyses will be performed.

- OS will be compared between treatment groups using a two-sided α (adjusted for the interim) unstratified log-rank test.

- OS will be compared between treatment groups using the strata as determined at baseline (CRF source). This analysis will be performed only if at least one stratification variable at IVRS and at baseline disagrees for at least 10% of the randomized subjects.

- OS will be compared between treatment groups using a two-sided α (adjusted for the interim) stratified log-rank test in the All Treated Subjects population, using arm as randomized. This analysis will be performed only if the proportion of randomized but never treated subjects exceeds 10%.

Estimate of the hazard ratio, its two sided $100(1-\alpha)\%$ CI (adjusted for the interim) and p-value will be presented.

7.5.1.3   *Consistency of Treatment Effect on OS in Subsets*

To assess consistency of treatment effects in different subsets, a "forest" plot of the OS unstratified hazard ratio (and 95% CI) will be produced for the following subgroups.

- CNS metastases (yes/no). (CRF source).
- Response to Platinum based Therapy (sensitive/resistant) (CRF source).
- Age category (< 65 - ≥ 65).
- Gender, Race, Region (US vs. Europe vs. Asia vs. Rest of World).
- Baseline ECOG PS.
- Baseline LDH ($\leq$ ULN vs. $>$ ULN).
- Disease Stage at initial diagnosis (extensive vs. limited).
- Time from Initial Disease Diagnosis to Randomization (< 1 year, Other).
- Best response to 1st line (CR/PR vs. SD vs. PD).
- Time from completion of 1st line therapy (< 3, $3 - 6$, > 6 months).

If subset category has less than 10 subjects per treatment group, HR will not be computed/displayed. Number of events and median OS along with 95% CI will be displayed for each treatment group.

7.5.1.4   *Multivariate Analysis*

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

- Age category (< 65 - ≥ 65).
- Gender

- Baseline ECOG PS,
- Disease Stage at initial diagnosis (extensive vs. limited)
- Time from Initial Disease Diagnosis to Randomization (< 1 year, Other).

HR and 95% CI will be provided for treatment variable and all covariates. Descriptive p-values will be provided.

7.5.1.5   Subject Follow-up for OS

The minimum follow-up will be reported. The minimum follow-up is defined as the time interval between the last patient's randomization date and the clinical cutoff date.

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

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. Subjects who died before data cut-off date will automatically have zero value for currentness of follow-up. For subjects with last known date alive after data cut-off date, they will have zero value for currentness of follow-up as well. The currentness of follow-up will be categorized into the following categories: 0 days, 1-3 months, 3-6 months, 6-9 months, 9-12 months and ≥ 12 months.

7.5.1.6   Follow-up Therapy

Subsequent therapies will be summarized and listed.

- Subsequent Therapy
    – Chemotherapy by drug name
    – Hormonal or biologic therapy by drug name
    – Immunotherapy (anti-PD1 agents, anti-CTLA4 agents and others, by drug name)
    – Tyrosine kinase inhibitor by drug name
    – Other investigational agent by drug name
    – Surgery
    – Radiotherapy
    – Any combination of the above
- By Subject Listing of Subsequent Therapy

7.5.1.7   Analysis of Survival by Tumor Response

Survival by response category will be analyzed by arm using the landmark method[16]. Subjects still on study at the landmark time will be separated into two response categories according to whether they have responded before that time. This will assess whether survival from the

landmark depends on the subject's response status at the landmark. Subjects who go off protocol (e.g. subjects who die) before the time of landmark will be excluded from the analysis.

The survival curves from Week 6, Month 4, Month 6, Month 8, Month 12, by response status, for each randomized arm will be produced using the KM product-limit method. Two sided, 95% confidence intervals for median OS will be constructed based on a log-log transformed CI for the survivor function S(t).

7.5.2   Progression Free Survival

7.5.2.1   Primary Analysis of PFS

PFS for each treatment arm will be estimated using Kaplan-Meier product limit method and graphically displayed. A two-sided 95% CI for median duration will be constructed based on a log-log transformed CI for the survivor function S(t) [9],[10] .

The comparison of PFS distribution will be performed via a stratified log-rank test at two-sided, 5% level. In addition, the stratified hazard ratios between treatment groups will be provided along with the 95% CI.

PFS rates at 6, 12, 18, 24, 36, 48 months and at 5 year will also be estimated using KM estimates on the PFS curve for each randomized arm. Minimum follow-up must be longer than or equal to timepoint to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood's formula[11].

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

The status of subjects who are censored in the PFS Kaplan-Meier analysis will be tabulated for each treatment group using following categories:
- Never treated
- On-study (on treatment, in follow-up)
- Off-study: (lost to follow-up, withdrew consent, other).
- Received subsequent anti-cancer therapy
- No baseline tumor assessment

To assess consistency of treatment effect on PFS in different subsets, a "forest" plot of the PFS unstratified hazard ratio (and 95% CI) will be produced for the same variable as in the OS analysis.

7.5.2.2   Sensitivity Analyses of PFS

Sensitivity analyses of PFS will also be performed using the following modification of PFS primary definition.
- PFS will be compared between treatment groups *using the strata as determined at baseline* (CRF source). This analysis will be performed only if at least one stratification variable at IVRS and at baseline disagrees for at least 10% of the randomized subjects.

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

- *PFS accounting for missing tumor assessment prior to PFS event (progression or death).* This analysis will be performed only if at least 20% of events have missing prior tumor assessment. It will apply the following restriction to the primary definition: If the elapsed time between the PFS event and the last on-study assessment immediately prior to the event (or randomization date if no on-study scan) is two or more missed visits (more than 12 weeks + 10 days), the subject will be censored at his last tumor assessment prior to the PFS event (or randomization date if no on-study scan).

- PFS *accounting for assessment after on-treatment palliative radiotherapy* . This analysis is similar to the primary analysis except that no censoring will occur for on-treatment palliative radiotherapy.

7.5.3   Objective Response Rate

7.5.3.1   Primary Analysis of ORR

BOR will be summarized by response category for each treatment group. ORR will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method[17].

An estimate of the difference in ORRs and corresponding 95% CI will be calculated using CMH methodology and adjusted by the same stratification factors as for primary analysis of OS.

In addition, the stratified (source: IVRS) odds ratios (Mantel-Haenszel estimator) between the treatments will be provided along with the 95% CI. The difference will be tested via the Cochran Mantel-Haenszel (CMH) test using a two-sided, 5% α level.

To assess consistency of treatment effect on ORR in different subsets, ORR will be computed across the same subsets as defined in the OS analysis (see Section 7.5.1.3).

7.5.3.2   Sensitivity Analyses of ORR

If one stratification variable at IVRS and at baseline (CRF) disagrees for at least 10% of the randomized subjects, similar analysis of ORR as primary analysis will be performed using the strata as determined at baseline.

7.5.4   Duration of Objective Response

Duration of response in each treatment group will be estimated using KM product-limit method for subjects who achieve PR or CR. Duration of stable disease will also be estimated in each treatment groups using KM product-limit method for subjects with SD as best response. Median values along with two-sided 95% CI will be calculated. Summary statistics will be computed constructed based on a log-log transformed CI for the survivor function S(t).

7.5.5   Time to Objective Response

Summary statistics of time to objective response will be provided for each treatment group for subjects who achieve PR or CR.

To assess further tumor response kinetics, time to response will be analyzed using the KM methodology, for all randomized subjects. Kaplan-Meier curve will represent the cumulative rate of response over time. For the non-responders, time to response will be censored at the maximum time of response + 1 day of all subjects in their respective treatment group. Cumulative Response Rates will be tabulated for Week 6, Month 4, 6, 8, and 12, and overall Response Rate will be provided for each treatment group.

7.5.6   Hierarchy for Key Secondary Efficacy Endpoints

In order to preserve an experimental-wise type I error rate at 5%, a pre-planned hierarchy for key secondary endpoints will be applied when interpreting the statistical significance of treatment comparisons. The hierarchical ordering of the key secondary endpoints is as follows:

1) Progression-Free Survival
2) Objective Response Rate

The statistical testing will be carried out using the following sequential procedure:

1) The primary endpoint of OS will be tested first.
2) If the p-value of OS is not statistically significant against nominal significance level either at interim or final analysis, then no further statistical testing regarding the secondary endpoints will be conducted. However estimates along with their 95% CI will be provided for those (i.e. medians and HR, rates and odds ratio)
3) If the p-value of OS is statistically significant against nominal significance level either at interim or final analysis, the secondary endpoint with the highest ranking in the hierarchy will be tested (PFS in this case). If the p-value of PFS is statistically significant at 5% level, the second highest ranking endpoint in the hierarchy will be tested (ORR in this case) and the p-value of ORR will be provided. If the p-value of PFS is not statistically significant at 5% level, then no further statistical testing regarding the other secondary endpoint (i.e., ORR) will be conducted. Estimates (medians and HR) and their 95% CI will be provided for ORR regardless of the outcome of PFS testing.

7.5.7   Follow-up Therapy

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

Subsequent therapies will be summarized and listed.

- Subsequent Therapy
  - Chemotherapy by drug name
  - Hormonal or biologic therapy by drug name
  - Immunotherapy (anti-PD1 agents, anti-CTLA4 agents and others, by drug name)

- Tyrosine kinase inhibitor by drug name
- Other investigational agent by drug name
- Surgery
- Radiotherapy
- Any combination of the above

- By Subject Listing of Subsequent Therapy

7.5.8   Other Efficacy Analyses

The following subject-level graphics will also be provided by treatment group as randomized:

- For the responders only, time courses of the following events of interest will be graphically displayed: tumor response, tumor progression, last dose received, and death.
- For response evaluable subjects, a waterfall plot showing the best reduction in target lesion will be produced.

7.5.9   Interim Analysis

No formal Analysis will be run

7.6   Safety

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   Adverse Events by Subgroups

See Core Safety SAP

7.6.7 Multiple Events

See Core Safety SAP

7.6.8 Adverse Events of Special Interest

See Core Safety SAP

7.6.9 Clinical Laboratory Evaluations

The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test.

7.6.9.1 Hematology

See Core Safety SAP

7.6.9.2 Serum Chemistry

See Core Safety SAP

7.6.10 Vital Signs and Pulse Oximetry

See Core Safety SAP

7.6.11 Immunogenicity Analysis

Nivolumab arm only. See Core Safety SAP

7.6.12 Pregnancy

By-subject listing of pregnancy tests results will be provided

7.6.13 Clinical Safety Program (CSP)

See Core Safety SAP

7.7 Pharmacokinetics

Pharmacokinetics analyses will be performed on nivolumab arm only.

The concentration vs. time data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). Model determined exposures will be used for exposure-response analyses of selected efficacy and safety end points. Results of population PK and exposure-response analyses will be reported separately.

7.8.1.3   Association between TMB and Efficacy

7.9   Outcomes Research Analyses

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

7.9.1   LCSS questionnaire

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

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

Kaplan-Meier plots for TTD in symptoms as measured by LCSS ASBI would be presented along with median TTD and corresponding 95% CI.

TTD rates at fixed timepoints Week 6, 12 and 24 will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula[18] for variance derivation and on log-log transformation applied on the survivor function S(t)[19].

7.9.2   EQ-5D questionnaire

AS done for LCSS, EQ-5D questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (i.e., the number of subjects still on treatment or in follow-up), will be calculated and summarized at each assessment point.

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

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

Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem and by treatment group, as randomized. Percentages will be based on number subjects assessed at assessment time point.

A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

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

8   CONVENTIONS

The following 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[20].
- Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in Section 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[21].

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive. If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive

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

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.
- In case of the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.
- For other partial/missing dates, the following conventions may be used:
- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

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

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

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

9 CONTENT OF REPORTS

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

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