Official Title: A Phase III, Randomized, Open-Label, Multicenter Study of Lurbinectedin in Combination with Atezolizumab Compared with Atezolizumab as Maintenance Therapy in Participants with Extensive-Stage Small-Cell Lung Cancer (ES-SCLC) Following First-Line Induction Therapy with Carboplatin, Etoposide and Atezolizumab

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: **A PHASE III, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY OF LURBINECTEDIN IN COMBINATION WITH ATEZOLIZUMAB COMPARED WITH ATEZOLIZUMAB AS MAINTENANCE THERAPY IN PARTICIPANTS WITH EXTENSIVE-STAGE SMALL-CELL LUNG CANCER (ES-SCLC) FOLLOWING FIRST-LINE INDUCTION THERAPY WITH CARBOPLATIN, ETOPOSIDE AND ATEZOLIZUMAB**

STUDY NUMBER: GO43104

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 2.0, 28 February 2022.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	See electronic date stamp on the last page of this document	Version 7, 11 December 2023

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ASTCT	American Society of Transplantation and Cellular Therapy
CI	confidence interval
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
DOR	duration of response
EC	ethics committee
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ES-SCLC	extensive-stage small-cell lung cancer
FA	final analysis
FAS	full analysis set
GHS	global health status
HR	hazard ratio
HRQoL	health related quality of life
IA	interim analysis
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IL46	item list 46
IRB	institutional review board
IRF	Independent Review Facility
IxRS	interactive voice/web-based response system
LDH	lactate dehydrogenase
MDD	minimum detectable difference
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NPT	non-protocol anti-cancer therapy
ORR	objective response rate
OS	overall survival

PCI	prophylactic cranial irradiation
PFS	progression-free survival
PR	partial response
PRO	Participant-reported outcomes
PRO CTCAE	Participant-Reported Outcomes Common Terminology Criteria for Adverse Events
PD	progressive disease
PK	Pharmacokinetic
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer Module
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumor
SAE	serious adverse events
SAP	Statistical Analysis Plan
SAS	safety analysis set
SD	stable disease
TTCD	time to confirmed deterioration
ULN	upper limit of normal

1. INTRODUCTION

The Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study GO43104 (IMforte), a Phase III, randomized, open-label, multicenter study of lurbinectidin in combination with atezolizumab compared with atezolizumab as maintenance therapy in participants with extensive-stage small-cell lung cancer (ES-SCLC) following first-line induction therapy with carboplatin, etoposide and atezolizumab. The background of the study can be found in the study protocol.

The analyses described in this SAP will supersede those specified in Protocol GO43104 for the purposes of a regulatory filing.

There are no changes to the planned analyses described in the protocol.

1.1 OBJECTIVES AND ENDPOINTS AND ESTIMANDS

The study will evaluate efficacy, safety, and pharmacokinetics of lurbinectedin when administered in combination with atezolizumab compared with atezolizumab monotherapy in participants with ES-SCLC, who have an ongoing response or stable disease (SD) after completion of 4 cycles of carboplatin, etoposide, and atezolizumab induction treatment. Table 1 presents the primary objectives for the study expressed using the estimands framework in accordance with the International Council for Harmonization (ICH) E9 (R1) statistical principles for clinical trials (ICH 2020). Table 2 presents the secondary and exploratory objectives and corresponding endpoints.

The term “study treatment” refers to all protocol-mandated treatments and includes atezolizumab in combination with carboplatin and etoposide during the induction phase, and atezolizumab, lurbinectedin, and protocol-mandated prophylactic medications (e.g., granulocyte colony-stimulating factor, anti-emetics) during the maintenance phase.

Most endpoints in Table 1 and Table 2 will be analyzed in randomized participants and therefore, the term “baseline” refers to the time of randomization into the maintenance phase, unless otherwise specified.

Table 1 Primary Objectives and Corresponding Estimands for Randomized Participants

Primary Objective(s)	Estimand Definition
• To evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab	• Population: individuals with ES-SCLC who have ongoing complete response (CR), partial response (PR) or SD after completion of 4 cycles of carboplatin, etoposide, and atezolizumab first-line induction treatment, as defined through the inclusion and exclusion criteria for the maintenance phase (see Protocol Section 5.1.2 and 5.2.2, respectively)

Primary Objective(s)	Estimand Definition
	• Variable: IRF-assessed progression-free survival (PFS) after randomization, defined as the time from randomization to the first occurrence of disease progression (as determined by IRF according to RECIST v1.1) or death, whichever occurs first • Treatment: – Experimental arm: atezolizumab 1200mg IV + lurbinectedin 3.2mg/m^2 IV on Day 1 of each 21-day cycle – Control arm: atezolizumab 1200 mg IV on Day 1 of each 21-day cycle • Intercurrent events and handling strategies: –Early discontinuation from study treatment for any reason: treatment policy strategy –Start of non-protocol anti-cancer therapy prior to the respective event of interest: treatment policy strategy • Population-level summary: hazard ratio (HR) for IRF-assessed PFS
• To evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab	• Population: as defined above • Variable: Overall survival (OS) after randomization, defined as the time from randomization to death from any cause • Treatment: as defined above • Intercurrent events and handling strategies: as defined above • Population-level summary: HR for OS

ES-SCLC = extensive-stage small-cell lung cancer; CR = complete response; HR = hazard ratio; IRF = independent review facility; IV = intravenous; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = response evaluation criteria in solid tumors; SD = stable disease.

Table 2 Secondary and Exploratory Objectives and Endpoints for Randomized Participants

Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab	• Investigator-assessed PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first • Confirmed objective response rate (ORR), defined as the proportion of randomized participants with a CR or PR on two consecutive occasions ≥ 4 weeks apart after randomization, as determined by the IRF according to RECIST v1.1 • Confirmed ORR, defined as the proportion of randomized participants with a CR or PR on two consecutive occasions ≥ 4 weeks apart after randomization, as determined by the investigator according to RECIST v1.1 • Duration of response (DOR), defined as the time from the first occurrence of a documented confirmed objective response after randomization until disease progression as determined by the IRF according to RECIST v1.1, or death from any cause, whichever occurs first • DOR, defined as the time from the first occurrence of a documented confirmed objective response after randomization until disease progression as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

Secondary Objectives	Corresponding Endpoints
•	• PFS rates at 6 months and 12 months, defined as the proportion of participants who have not experienced disease progression, as determined by the IRF according to RECIST v1.1, or death from any cause at 6 months and 12 months after randomization • PFS rates at 6 months and 12 months, defined as the proportion of participants who have not experienced disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause at 6 months and 12 months after randomization • OS rates at 12 months and 24 months, defined as the proportion of participants who have not experienced death from any cause at 12 months and 24 months after randomization
• To evaluate the safety of lurbinectedin in combination with atezolizumab compared with atezolizumab	• Incidence and severity of adverse events, including serious adverse events and adverse events of special interest, with severity determined according to NCI CTCAE v5.0
• To evaluate the health–related quality of life of participants treated with lurbinectedin in combination with atezolizumab compared with atezolizumab	• Time to confirmed deterioration (TTCD) from randomization in participant-reported physical functioning and global health status as measured by the EORTC QLQ-C30
• To evaluate the immunogenicity of atezolizumab with and without lurbinectedin	• Prevalence of ADAs to atezolizumab at induction phase baseline and incidence of ADAs to atezolizumab after drug administration
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of lurbinectedin in combination with atezolizumab compared with atezolizumab	• Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results

Secondary Objectives	Corresponding Endpoints
• To evaluate the tolerability of lurbinectedin in combination with atezolizumab compared with atezolizumab from the participant's perspective	• Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities as assessed through use of the NCI PRO-CTCAE • Change from baseline in severity of selected symptomatic treatment toxicities, as assessed through use of the NCI PRO-CTCAE • Frequency of response by arm and by time point of the EORTC IL46 single item for bothered by treatment effects
• To evaluate the health-related quality of life of participants treated with lurbinectedin in combination with atezolizumab compared with atezolizumab	• Change from baseline in PROs of HRQoL, physical function and global health status as assessed by the EORTC QLQ-C30 • Change from baseline in lung cancer-related symptoms as assessed by the EORTC QLQ-LC13
• To characterize the PK profile of lurbinectedin and atezolizumab	• Plasma concentration of lurbinectedin at specific timepoints • Serum concentration of atezolizumab at specific timepoints
• To evaluate the potential effects of atezolizumab immunogenicity	• Relationship between atezolizumab ADA status and efficacy, safety, or PK endpoints
• [redacted]	[redacted]

ADA = anti-drug antibody; CR = complete response; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; HRQoL = health-related quality of life; IL46 = item list 46; IRF = independent review facility; LC13 = lung cancer 13; NCI = National Cancer Institute; CTCAE v5.0 = Common Terminology Criteria for Adverse Events, Version 5; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PR = partial response; PRO = Participant-Reported Outcome; PRO-CTCAE = Participant-Reported Outcome Common Terminology Criteria for Adverse Events; PK = pharmacokinetic; QLQ-C30 = Quality of Life Questionnaire-Core 30; RECIST = Response Evaluation Criteria in Solid Tumors; TTCD = time to confirmed deterioration

1.2 STUDY DESIGN

Study GO43104 is a Phase III, randomized, open-label, multicenter study of lurbinectedin in combination with atezolizumab compared with atezolizumab alone

administered as maintenance therapy in participants with ES-SCLC after first-line induction therapy with carboplatin, etoposide, and atezolizumab. Participants are required to have an ongoing response or SD per the Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 after completion of 4 cycles of carboplatin, etoposide, and atezolizumab induction treatment in order to be considered for eligibility screening for the maintenance phase.

The study consists of 2 phases: an induction phase and a maintenance phase.

Participants who have been diagnosed with ES-SCLC and are treatment-naïve for their extensive-stage disease have to provide written informed consent prior to entering screening for the induction phase (induction screening). Participants who fulfill the eligibility criteria (see protocol Section 5.1 and 5.2) will be enrolled to receive 4 cycles of carboplatin, etoposide and atezolizumab induction treatment. The diagnosis of ES-SCLC will be based on the Veterans Administration Lung Study Group staging system (see protocol Appendix 17). Participants will receive 4 cycles of induction treatment unless they experience unacceptable toxicity or disease progression or they withdraw consent.

Participants must fulfill the eligibility criteria for the maintenance phase (see protocol Section 5.1.2 and 5.2.2) prior to randomization (maintenance screening). Participants who have received fewer than 4 or more cycles of carboplatin, etoposide and atezolizumab as induction, or experience progressive disease (PD) during the induction phase will not be eligible for the maintenance phase.

Following the induction therapy but before randomization, participants may receive prophylactic cranial irradiation (PCI) at the investigator's discretion per local standard. In accordance with National Comprehensive Cancer Network (NCCN) guidelines, magnetic response imaging (MRI) surveillance can be considered as an alternative option to PCI (National Comprehensive Cancer Network 2021).

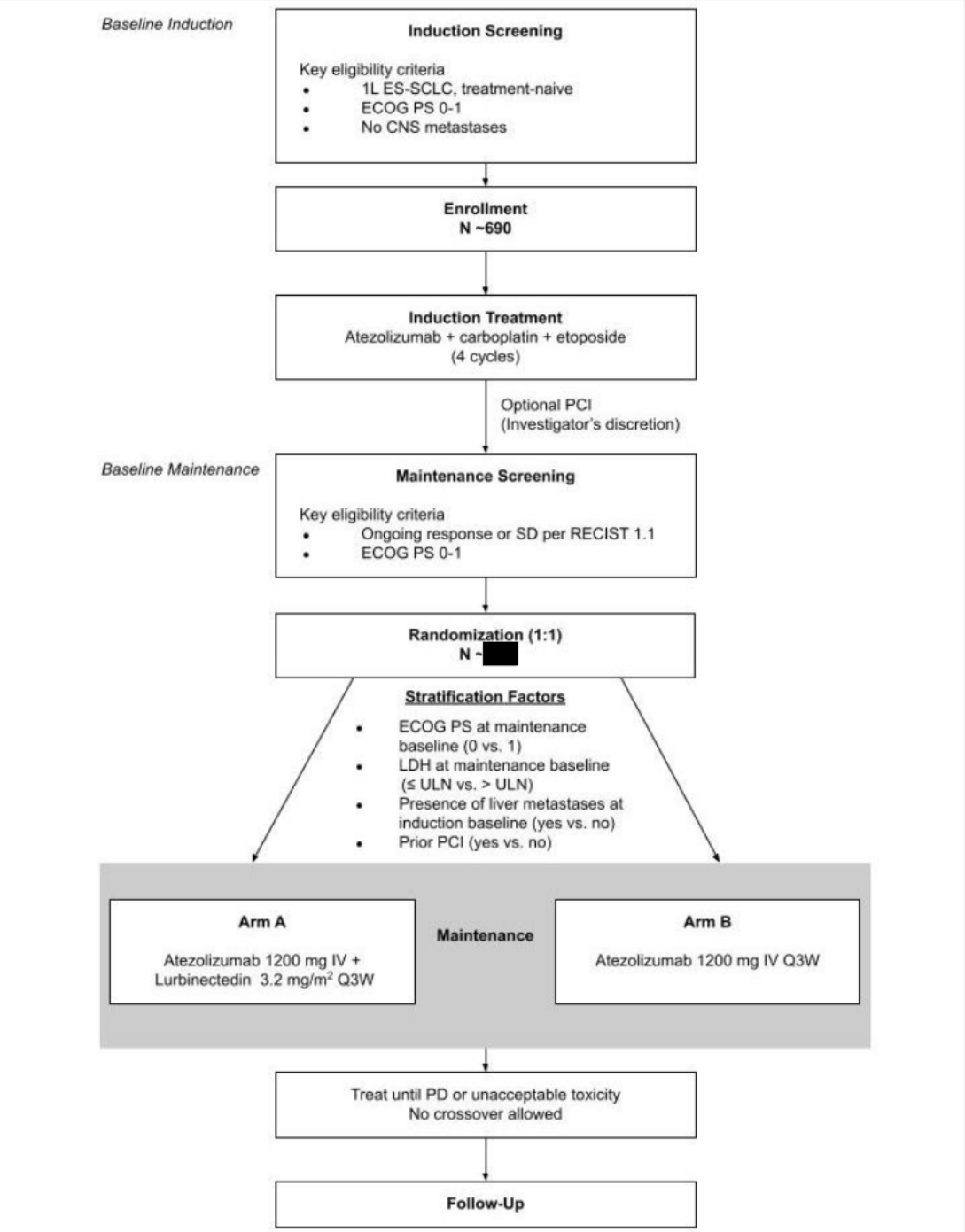
Participants who receive consolidative thoracic radiation with curative intent or the intent to eliminate residual disease or participants with lesions that require palliative radiotherapy are not eligible for the maintenance phase of this study.

Randomization must occur within 5 weeks (35 days) from the day of the administration of the last dose of atezolizumab, carboplatin and/or etoposide (whichever occurs last). Participants receiving PCI must be randomized within 9 weeks (63 days) from the last dose of atezolizumab, carboplatin and/or etoposide (whichever occurs last).

In order not to confound the evaluation of overall survival (OS), crossover will not be allowed from Arm B (atezolizumab) to Arm A (atezolizumab in combination with lurbinectedin).

The study schema is shown in Figure 1.

Figure 1 Study Schema



1L = first-line; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ES-SCLC = extensive-stage small-cell lung cancer; IV = intravenous; LDH = lactate dehydrogenase; PCI = prophylactic cranial irradiation; PD = progressive disease; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; ULN = upper limit of normal.

1.2.1 Treatment Assignment and Blinding

This is a randomized, open-label study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participants' study identification number from the interactive voice or Web-based response system (IxRS). For those participants who are eligible for randomization into the maintenance phase of the study, the study site will obtain the participant's randomization number and treatment assignment from the IxRS once eligibility has been established during the maintenance screening.

Participants will be randomly assigned to one of the two treatment arms: A) atezolizumab + lurbinectedin or B) atezolizumab. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by:

- Eastern Cooperative Oncology Group Performance Status at maintenance baseline (0 vs. 1)
- Lactate dehydrogenase at maintenance baseline (≤ ULN vs > ULN) via local laboratory test
- Presence of liver metastases at induction baseline (yes vs. no)
- Prior receipt of PCI (yes vs. no)

Although this is an open-label study, the randomized treatment assignments from the IxRS will be withheld from members of the Sponsor, including, but not limited to, the study's Medical Monitor, Study Statistician, Statistical Programmer, and Study Data Manager. Members of the Sponsor are not permitted to perform analyses or summaries by randomized treatment assignment and/or actual treatment received before the randomized treatment assignments are disclosed to the study team for the pre-specified analysis.

1.2.2 Independent Review Facility

An independent review facility (IRF) will perform a centralized, independent central review of images, and other clinical data as needed, prior to the efficacy analyses. IRF membership and procedures are detailed in an IRF charter.

1.2.3 Data Monitoring

An independent Data Monitoring Committee (iDMC) will evaluate safety data during the study. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC's roles and responsibilities.

Safety data will be reviewed on a periodic basis starting after approximately 24 participants have completed 2 cycles of maintenance treatment or 6 months from the time of the first participant randomized into the maintenance phase, whichever is earlier, and approximately every 6 months thereafter until the randomized treatment assignment

information is disclosed to the study team for the pre-specified analyses. All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center.

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards (IRBs)/ Ethics Committees (ECs).

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

The purpose of this study is hypothesis testing and estimation regarding the effect of lurbinectedin in combination with atezolizumab on the duration of IRF-assessed progression-free survival (PFS) and/or OS compared with atezolizumab alone. The primary objective of this study is to evaluate the efficacy of lurbinectedin in combination with atezolizumab compared with atezolizumab. The primary endpoints for this study are OS and IRF-assessed PFS in the full analysis set (FAS).

The null and alternative hypotheses regarding IRF-assessed PFS or OS in the FAS can be phrased in terms of the survival function, the IRF-assessed PFS or OS survival functions $S_A(t)$ for lurbinectedin in combination with atezolizumab and $S_B(t)$ for atezolizumab.

$$H_0: S_A(t) = S_B(t) \text{ versus } H_1: S_A(t) \neq S_B(t)$$

2.2 SAMPLE SIZE DETERMINATION

Approximately 920 participants will be screened to achieve the enrollment of approximately 690 participants into the induction phase. Approximately [redacted] participants will be randomized into this study for an estimated total of [redacted] participants per treatment group.

2.2.1 Type I Error Control

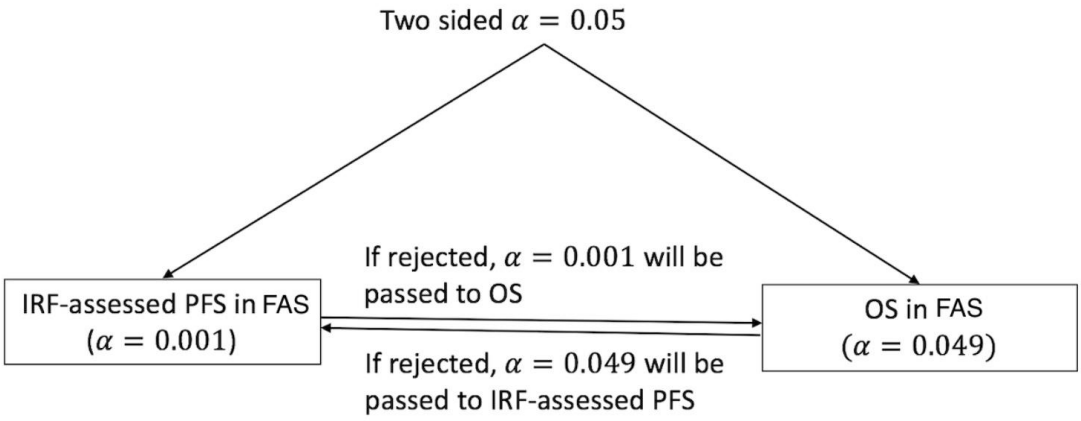
The overall type I error (α) for this study is 0.05 (2-sided) and will be controlled for the primary endpoints of OS and IRF-assessed PFS according to RECIST v1.1 in the FAS with use of a group sequential weighted Holm procedure (Ye et al. 2013). A 2-sided $\alpha = 0.049$ and a 2-sided $\alpha = 0.001$ are allocated to OS and IRF-assessed PFS, respectively.

An alpha recycling from IRF-assessed PFS to OS will be conducted as follows: if the IRF-assessed PFS comparison is not statistically significant at a 2-sided $\alpha = 0.001$, the

primary comparison of OS will be tested at a 2-sided $\alpha = 0.049$; if the IRF-assessed PFS comparison is statistically significant at the 2-sided $\alpha = 0.001$, OS will be tested at a 2-sided $\alpha = 0.05$. Additionally, if OS is statistically significant at the 2-sided $\alpha = 0.049$, IRF-assessed PFS will be tested at a 2-sided $\alpha = 0.05$.

The overview of the type I error rate control strategy is shown in Figure 2 below.

Figure 2 Type 1 Error Rate Control Strategy



FAS = Full Analysis Set; IRF-assessed PFS = Independent Review Facility- assessed progression-free survival; OS = overall survival.

2.2.2 Overall Survival

The sample size determination is based on the number of events required to demonstrate efficacy with regard to OS in the FAS. The estimate of the number of events required is based on the following assumptions:

- 1:1 randomization ratio
- Two-sided significance level of 0.049 for the comparison of OS
- Approximately 85% power to detect an hazard ratio (HR)= 0.71 in OS, corresponding to an improvement in median OS from 12.5 months to 17.6 months in the FAS
- One planned interim analysis for OS at approximately 68% of the information fraction, with the stopping boundary determined by the Hwang-Shih-DeCani alpha spending function with the gamma parameter of -1.5 (Hwang et al. 1990)
- Dropout rate of 5% over 24 months for each treatment arm for OS

With these assumptions, the final OS analysis will occur when approximately 323 deaths (72% of [redacted] randomized participants) have been observed in the FAS. With these assumptions, the minimum detectable difference (MDD) in HR is approximately 0.793 for the final OS analysis. The final OS analysis is expected to occur approximately 41 months after the first patient is randomized.

2.2.3 IRF-assessed PFS

The primary IRF-assessed PFS analysis will be conducted at the time of the OS interim analysis when approximately 219 deaths in the FAS have been observed or when the minimum follow-up has been completed, whichever occurs later. The minimum follow-up is defined as 5 months after the target sample size of 450 participants has been randomized, or 5 months after the last participant has been randomized in case the final sample size is lower than 450 participants.

At the time of the OS interim analysis, it is estimated that approximately 392 IRF-assessed PFS events in the FAS will have occurred. This number of events provides more than 99% power to detect an HR = 0.5 in IRF-assessed PFS at a 2-sided significance level of 0.001, based on the following assumptions:

- 1:1 randomization ratio
- Median PFS of 2.6 months in the atezolizumab arm and 5.2 months in the atezolizumab + lurbinectedin arm (corresponding to a target HR = 0.5)
- Dropout rate of 5% over 12 months for PFS
- No interim analysis for PFS

With these assumptions, the MDD in HR is approximately 0.72 for the IRF-assessed PFS analysis in the FAS.

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 3.

Table 3 Participant Analysis Sets

Participant Analysis Set	Description
FAS	All participants randomized into the maintenance phase regardless of whether or not the assigned study treatment is received: participants will be included in the analyses according to the treatment to which they were assigned by IxRS at randomization
SAS	All participants who are randomized into the maintenance phase and receive at least 1 dose of atezolizumab or lurbinectedin: participants will be analyzed according to the treatment that they received, i.e., participants who receive lurbinectedin in error will be analyzed in Arm A for the SAS
Enrolled analysis set	All participants who are enrolled in the induction phase, regardless of whether or not they receive induction treatment and regardless of whether they are subsequently randomized
Enrolled SAS	All enrolled participants, who receive at least 1 dose of atezolizumab or carboplatin or etoposide, regardless of whether or not they are subsequently randomized

FAS = full analysis set; IxRS = interactive voice/web-based response system; SAS = safety analysis set

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

Unless otherwise specified, all efficacy analyses will be performed in the FAS. Participants will be analyzed according to the treatment assigned at randomization by IxRS.

Unless otherwise specified, all safety analyses will be performed in the safety analysis set (SAS). Participants will be analyzed according to the treatment they actually received. Specifically, a participant will be included in the atezolizumab and lurbinectedin combination arm in the safety analyses if the participant receives any amount of lurbinectedin, regardless of the initial treatment assignment at randomization.

Unless otherwise specified, baseline measurements are the last available data obtained prior to the participant receiving the first dose of any component of protocol treatment in the maintenance phase.

4.2 PRIMARY ESTIMANDS ANALYSIS

4.2.1 Definition of Primary Estimands

The primary objective for this study is to evaluate the efficacy of lurbinectedin when administered in combination with atezolizumab compared with atezolizumab monotherapy in participants with ES-SCLC, who have an ongoing response or SD after completion of 4 cycles of carboplatin, etoposide, and atezolizumab induction treatment on the basis of primary endpoints: IRF-assessed PFS according to RECIST v1.1 and OS, as defined in Section 1.1 (see Table 1) in estimands framework.

4.2.2 Main Analytical Approach for Primary Estimands

For IRF-assessed PFS, participants who have not experienced disease progression and have not died by the clinical cutoff date will be censored at the time of the last tumor assessment. Participants who have no tumor assessment after baseline and have not died by the clinical cutoff date will be censored at the date of randomization.

For OS, participants who are not reported as having died by the clinical cutoff date will be censored at the date when they were last known to be alive. Participants who do not have information after baseline will be censored at the date of randomization. Participants who are lost to follow-up will be censored at the last date they were known to be alive for the primary analysis of OS.

Each of the primary endpoints will be compared between two treatment arms based on the stratified log-rank test. The HR will be estimated with use of a stratified Cox regression model, including two-sided 95% confidence intervals (CIs). The stratification factors will be those used for randomization (as listed in Section 1.2.1). The Kaplan-Meier methodology will be used to estimate the median IRF-assessed PFS and median OS for each treatment arm, and Kaplan-Meier curves will be constructed to provide a

visual description of the difference between treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CIs for the median IRF-assessed PFS and median OS for each treatment arm (Brookmeyer and Crowley 1982). Results from an unstratified analysis will also be provided.

4.2.3 Sensitivity Analyses

If >5% of participants are lost to follow-up for OS in either treatment arm, a sensitivity analysis will be performed for the comparisons between two treatment arms in which participants who are lost to follow-up will be considered as having died at the last date they were known to be alive.

The impact of missing scheduled tumor assessments on IRF-assessed PFS will be assessed depending on the number of participants who missed tumor assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or the data cutoff. If >5% of participants missed two or more consecutive assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or the data cutoff in any treatment arm, the following sensitivity analysis will be performed:

- Participants who missed two or more consecutive scheduled assessments immediately prior to the date of disease progression per RECIST v1.1 or death will be censored at the last tumor assessment prior to the missed visit.

4.2.4 Supplementary Analyses

The following supplementary analyses will be performed for the primary efficacy endpoints of OS and IRF-assessed PFS in which a different handling rule of intercurrent events is implemented to provide further understanding of the treatment effect.

To assess the impact of the intercurrent event of starting a non-protocol anti-cancer therapy (NPT) prior to a PFS event, the primary analysis of IRF-assessed PFS will be repeated with such intercurrent event handled using a hypothetical strategy, if >5% of participants received NPT prior to a PFS event in either treatment arm. To estimate the estimand that implements this strategy, participants who start an NPT before a PFS event will be censored at the time of the last tumor assessment before the initiation of NPT.

To assess the impact of the intercurrent event of starting an NPT on OS, the primary analysis of OS will be repeated with such intercurrent event handled using a hypothetical strategy if >10% of participants received NPT in either treatment arm. The discounted method uses a “discounted” survival time after NPT usage for patients who received NPT based on a user-specified assumption for the effect in OS. The duration from initiation of NPT to death or censoring date may be discounted according to a range of possible effects on OS of the subsequent NPT (e.g., 10%, 20%, 30%, etc). After adjustments are made for the effect of subsequent NPT on OS, the methods that are outlined for OS in Section 4.2.2 will be used for these analyses.

4.2.4.1 Subgroup Analyses for Primary Endpoints

The generalizability of OS and IRF-assessed PFS results when comparing the experimental arm to the control arm will be investigated by estimating the treatment effect in subgroups defined by demographics and prognostic characteristics, including but not limited to: age, sex, race, ethnicity, ECOG performance status at maintenance baseline, smoking status, LDH at maintenance baseline, presence of liver metastases at induction baseline and prior receipt of PCI.

Summaries of OS and IRF-assessed PFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median OS and PFS, will be provided in forest plots.

4.3 SECONDARY ENDPOINTS ANALYSES

4.3.1 Investigator-Assessed PFS

Investigator-assessed PFS is defined as the time from randomization to the date of first documented disease progression as assessed by the investigator according to RECIST v1.1 or death, whichever occurs first. Participants who have not experienced disease progression and have not died by the clinical cutoff date will be censored at the time of the last tumor assessment. Participants with no tumor assessment after baseline will be censored at the date of randomization.

Investigator-assessed PFS will be analyzed through use of the same methods described for the IRF-assessed PFS analysis (see Section 4.2.2).

4.3.2 Confirmed Objective Response Rate

A confirmed objective response is defined as either a complete response (CR) or a partial response (PR) on two consecutive occasions ≥ 4 weeks apart after randomization, as determined by the IRF according to RECIST v1.1. Participants not meeting these criteria, including participants without any post-baseline tumor assessment, will be considered non-responders.

The analysis set for confirmed objective response rate (ORR) will be the FAS with measurable disease at baseline. An estimate of confirmed ORR and its 95% CI will be calculated with use of the Clopper Pearson method for each treatment arm. Confidence intervals for the difference in confirmed ORRs between the two treatment arms will be determined with use of the normal approximation to the binomial distribution.

The investigator-assessed confirmed ORR will also be analyzed through the same methods as described above.

4.3.3 Duration of Response

Duration of response (DOR) will be assessed in participants who had a confirmed objective response as determined by the IRF according to RECIST v1.1 in the FAS. Duration of response is defined as the time interval from the date of the first occurrence

of a documented confirmed objective response until the first date of progressive disease (PD) as determined by the IRF according to RECIST v1.1 or death is documented, whichever occurs first. Participants who have not progressed and who have not died at the time of analysis will be censored at the time of the last tumor assessment date. Duration of response is based on a non-randomized subset of participants (specifically, participants who achieved a confirmed objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes.

Duration of response (for participants with confirmed objective response), as determined by the investigator according to RECIST v1.1, will also be analyzed.

The methodologies detailed for the PFS analysis will be used for the DOR analysis.

4.3.4 Progression-Free Survival and Overall Survival Rates at Landmark Timepoints

The IRF-assessed and investigator-assessed PFS rates at 6 months and at 12 months after randomization will be estimated with use of the Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated with use of the standard error derived from Greenwood's formula. The 95% CI for the difference in PFS rates between the two treatment arms will be estimated with use of the normal approximation method.

Similar analyses will be performed for the OS rates at 12 months and 24 months after randomization.

4.3.5 Incidence and Severity of Adverse Events

The secondary safety objective will be assessed through summaries of the incidence and severity of treatment-emergent adverse events (AEs) in the SAS.

Verbatim description of adverse events will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. Severity for all adverse events will be graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Severity for Cytokine release syndrome (CRS) will also be graded by the investigator according to the American Society of Transplantation and Cellular Therapy (ASTCT) consensus grading scale. All adverse events will be summarized by treatment arm and NCI CTCAE grade. Cytokine release syndrome will also be summarized by treatment arm and the ASTCT consensus grade. All adverse events, Grade 3-4 adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, adverse events leading to treatment interruption/modification and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by preferred term, system organ class, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Multiple occurrences of the same event in the same patient will

be counted once at the maximum severity. Deaths and cause of death will be summarized.

4.3.6 Time to Confirmed Deterioration

Confirmed clinically meaningful deterioration for physical functioning and Global Health Status (GHS)/Quality of Life (QoL) is defined as a clinically meaningful decrease from baseline in the physical functioning or GHS/QoL scores that must be held for at least two consecutive assessments or an initial clinically meaningful decrease above baseline followed by death attributable to cancer progression within 6 weeks of the last deteriorated PRO assessment. A score change of ≥ 10-point change in GHS/QoL and functional subscale scores is perceived by participants as clinically meaningful (Osoba et al. 1998).

For time to confirmed deterioration (TTCD), data for participants will be censored at the last time when they completed an assessment if they have not experienced a confirmed clinically meaningful deterioration at the clinical cutoff date. If no baseline or post-baseline assessment is performed, participants will be censored at the randomization date. According to the while-on-treatment/while-alive strategy, participants who die before reporting any clinically meaningful deterioration will be censored at the last time they completed an assessment. Time to confirmed deterioration using the European Organization for Research and Treatment of Cancer (EORTC) scale will be analyzed with use of the same methods as for PFS.

[redacted]

4.4 EXPLORATORY ENDPOINTS ANALYSES

4.4.1 Laboratory data and Vital signs

Selected laboratory data will be graded according to NCI CTCAE v5.0 and will be summarized by treatment arm with shift tables from baseline to worst post baseline value. Changes in vital signs will also be summarized.

[redacted]

[redacted]

4.4.4 Clinical Outcome Assessment Analyses

Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) and the mean change from baseline of linear-transformed scores will be reported for all of the items and scales of the EORTC quality of life questionnaire core 30 (QLQ-C30) and EORTC QLQ-LC13 (lung cancer-specific subset) questionnaires according to the EORTC scoring manual guidelines. These will be reported separately for the induction period and the maintenance period, with baseline being defined as Cycle 1 Day1(C1D1) for each period.

Patient-Reported-Outcome-CTCAE (tolerability as measured by severity, frequency and/or interference of relevant events) and EORTC IL46 (a single item for level of bothersome experienced from treatment) analyses will be conducted in the SAS. Analyses will be descriptive (frequency counts and percentages). For the Participant Reported Outcome-common Terminology Criteria for Adverse Events (PRO-CTCAE), there will be a focus on characterizing the pattern of symptomatic treatment toxicities during the study. The EORTC IL46 and PRO-CTCAE data will be summarized at the item level. For each treatment arm, the number and percentage of participants reporting symptom by “frequency”, “severity”, “interference” and “presence” category will be reported at each assessment. A summary table of the percentage of participants reporting severity of a symptom as “severe” or “very severe” over the course of the study by treatment arm will also be provided. Change from baseline of severity for PRO-CTCAE selected items will be summarized separately for the induction and maintenance periods. Finally, a longitudinal analysis of change may be employed to understand how symptoms may have changed over the course of treatment. Results from these exploratory analyses will be presented separately from other safety analyses. EORTC IL46 will be summarized as frequencies by treatment arm and by timepoint. Some of those exploratory analyses might not be included in the Clinical Study Report (CSR).

Completion rates of questionnaires will be summarized at each timepoint by treatment arm.

[redacted]

4.5 OTHER SAFETY ANALYSES

4.5.1 Extent of Exposure

Drug exposure will be summarized during the maintenance phase in the SAS, including duration, dosage, and dose intensity.

Additionally, drug exposure of atezolizumab and chemotherapy during the induction phase will be summarized to include number of doses and dose intensity with use of descriptive statistics for the enrolled SAS.

4.5.2 Adverse events

AEs, serious AEs, and death (cause of death) during the induction phase will be summarized for the enrolled SAS.

4.5.3 Additional Safety Assessments

4.5.3.1 Laboratory Data and Vital Signs

Laboratory data with values outside of the normal ranges will be identified. Vital signs may also be summarized by treatment arm and visit.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

Study enrollment, study drug administration, reasons for discontinuation from the study treatment, and reasons for study discontinuation will be summarized for the enrolled analysis set, the enrolled SAS, the FAS, or the SAS by treatment arm as appropriate. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will be reported and summarized for the enrolled analysis set and for the FAS by treatment arm.

4.6.2 Summaries of Demographics and Baseline Characteristics

Demographics (e.g., sex, age) and baseline characteristics (e.g., ECOG Performance Score, LDH) will be summarized for the FAS by treatment arm. Baseline measurements are the last available data obtained prior to the participant receiving the first dose of any component of protocol treatment in the maintenance phase, unless otherwise noted. Descriptive statistics (mean, standard deviation, median and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

[redacted]

[redacted]

[redacted]

5. SUPPORTING DOCUMENTATION

This section is not applicable since there is no additional supporting document.

6. REFERENCES

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